National Research Centre for the Working Environment

CABIN AIR QUALITY III

Toxicological assessment plan

Data review, toxicological hazard identification and recommendations for risk assessment in CAQ III

Karin Sørig Hougaard, Niels Hadrup, Ulla Vogel, Anne Thoustrup Saber, together with the research group

National Research Centre for the Working Environment, Copenhagen, Denmark

Cabin Air Quality Research Workshop
17-18 January 2023

Toxicological and hazard identification assessment plan

Provide scientific data to identify chemical compounds during oil-related fume events and their health effects

Hazardardous chemicals:
Chemical with the potential to induce harmful health effects in humans

- Collect contaminant measurement data from existing datasets
- Compare of existing measurement data with newly identified indicator compounds to identify indicator compounds for oil contamination
- Collect toxicological data for measured contaminants
- Identify gaps in toxicological data
- Recommendations for complete hazard identification and risk assessment in future settings

WP1 FLOW and input from partners, scientific committe and stakeholders

Task 1.1

<u>Collect data on air cabin contaminants</u> from existing datasets ("Baseline")

<u>Point-of-departure:</u>
Chen et al. 2021: Cabin air quality on non-smoking commercial flights;
additional searches;
stakeholder input

CABIN AIR QUALITY III

Collect contaminant measurement data from existing datasets

Based on peer reviewed papers in international journals on fíeld measurements

Point of departure

REVIEW ARTICLE

WILEY

Cabin air quality on non-smoking commercial flights: A review of published data on airborne pollutants

Ruiqing Chen[1] | Lei Fang[2] | Junjie Liu[1] | Britta Herbig[3] | Victor Norrefeldt[4] | Florian Mayer[4] | Richard Fox[5] | Pawel Wargocki[2]

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Abstract

We reviewed 47 documents published 1967–2019 that reported measurements of volatile organic compounds (VOCs) on commercial aircraft. We compared the meas-

Additional searches retrieved:

Received: 26 March 2021 | Revised: 23 June 2021 | Accepted: 24 June 2021

DOI: 10.1111/ina.12903

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Michaelis *et al. Environ Health* (2021) 20:89
https://doi.org/10.1186/s12940-021-00770-7

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Received: 1 December 2020 | Revised: 26 January 2021 | Accepted: 13 February 2021

DOI: 10.1111/ina.12812

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Building and Environment 153 (2019) 118–127

Contents lists available at ScienceDirect

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Environment International 158 (2022) 106999

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

ELSEVIER

Identification of key volatile organic compounds in aircraft cabins and associated inhalation health risks

Yihui Yin [a,1], Junzhou He [b,1], Lei Zhao [a], Jingjing Pei [a,*], Xudong Yang [b], Yuexia Sun [a], Xikang Cui [c], Chao-Hsin Lin [d], Daniel Wei [e], Qingyan Chen [f]

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ARTICLE INFO

ABSTRACT

Status of database of measured contaminants:

Version 1 finalised with

1) Substances from Chen et al.

Chen (All non-smoking flights) | New Studies (Substances) | New Studies (Particles)

	Chen et al. Non-smoking flights		Active sampling measurements (S6)					Passive sampling measurements (S7)					Canister Sampling measurements (S5)				
	Compounds	Chemical Abstract System (CAS) no.	Concentration(μg/m³)			Number of		Concentration(μg/m³)			Number of		Concentration(μg/m³)			Number of	
			Avg.	Min.	Max.	studies	flights	Avg.	Min.	Max.	studies	flights	Avg.	Min.	Max.	studies	flights
4	(-)-Camphene												1.0	NC	NC	1	2
5	1,1,1-Trichloroethane	71-55-6	0.1	0.0	1.9	1	63	NC	NC	NC	1	4	0.0	0.0	5.0	3	73
6	1,1,2,2-Tetrachloroethane	79-34-5						NC	NC	NC	1	4	0.0	0.0	0.1	2	24
7	1,1,2-Trichloro-1,2,2-trifluoroethane	76-13-1											0.0	0.0	0.0	1	20
8	1,1,2-Trichloroethane	79-00-5						NC	NC	NC	1	4	0.3	NC	NC	3	26
9	1,1-Dichloroethane	75-34-3						NC	NC	NC	1	4	0.0	0.0	0.0	2	24
10	1,1-Dichloroethene	25101-06-8											0.0	0.0	0.0	2	24
11	1,1'-Dipropane-1,2-diol ether	110-98-5	1.5	0.0	124	1	69										
12	1,2,4-Trichlorobenzene	120-82-1						NC	NC	NC	1	4	0.0	0.0	0.7	2	24
13	1,2,4-Trimethylbenzene	95-63-6	0.4	0.0	5.1	1	5	<1.3	0.0	2.9	2	5	24	0.0	53	3	73
14	1,2-Dibromoethane	106-93-4						0.1	0.0	0.8	1	4	0.0	0.0	0.0	2	24
15	1,2-Dichlorobenzene	95-50-1											0.0	0.0	0.1	1	20
16	1,2-Dichlorobthane	107-06-2	0.4	<LOD	10	1	51										
17	1,2-Dichloroethane	107-06-2						NC	NC	NC	1	4	1.1	NC	NC	3	26
18	1,2-Dichloroethene(c)	540-59-0						NC	NC	NC	1	4					
19	1,2-Dichloroethene(t)	540-59-0						NC	NC	NC	1	4					
20	1,2-Dichloropropane	78-87-5						NC	NC	NC	1	4	0.0	0.0	0.0	2	24
21	1,2'-Dipropane-1,2-diol ether	NO	1.4	0.0	115	1	69										
22	1,2-Propanediol	57-55-6	41	0.0	363	1	69										
23	1,2-Dichlorotetrafluoroethane	76-14-2											0.0	0.0	0.0	1	2
24	1,3,5-Trimethylbenzene	108-67-8	0.5	0.0	42	1	5	0.4	0.0	2.0	1	4	0.1	0.0	0.5	2	24
25	1,3-Dichloropropene	10061-01-5/10061-02-6						NC	NC	NC	1	4					
26	1,3-Butadiene	106-99-0	0.6	0.0	213	1	63						0.0	0.0	0.0	2	24
27	1,3-Butanediol	107-88-0	4.6	0.0	70	1	69										
28	1,4-Dioxane	123-91-1						NC	NC	NC	1	4	0.0	0.0	0.0	2	24
29	1-Butanol	71-36-3	2.2	0.1	32	1	69						3.0	NC	NC	1	2
30	1-Hexanol,2-ethyl-	103-09-3	7.8	4.8	12	1	14										
31	1-Methoxy-2-propylacetate/propylene glycol m	108-65-6	0.9	0.0	9.7	1	69										
32	1-Propanol	71-23-8	71	0.0	1524	1	69										
33	2,2,4,4,6,8,8-Heptamethyl nonane	09-04-4390	2.2	0.0	49	1	69										
34	2,2,4,6,6-Pentamethyl heptane	13475-82-6	2.6	0.0	61	1	69										
35	2,2,4-Trimethyl pentane	540-84-1	0.1	0.0	2.3	1	69										
36	2,2,4-Trimethylpentane dioldiisobutyrate	NO	1.1	0.0	69	2	152										
37	2,3-Dimethylpentane	565-59-3	0.1	0.0	9.5	1	63						5.0	NC	NC	1	2
38	2,5-Dimethylbenzaldehyde	5779-94-2	0.6	0.1	2.1	1	108										
39	2,5-Diphenylbenzoquinone	844-51-9						<2.1	NR	NR	1	1					
40	2-Ethyl-1-hexanol/2-Ethylhexanol	104-76-7	4.7	0.1	30	2	120										
41	2-Ethylhexanal	123-05-7											30	NC	NC	1	2
42	2-Ethylhexyl salicylate	118-60-5	2.1	0.0	19	1	69										
43	2-Hexanone	591-78-6											0.2	0.0	0.3	2	22
44	2-Methylhexane	591-76-4											10	NC	NC	1	2
45	2-Hydroxybenzaldehyde	90-02-8	0.5	0.0	8.0	1	69										
46	2-Methylhexane	591-76-4	0.2	0.0	17	1	63										
47	2-Methylpentane	107-83-5	1.3	0.0	393	1	63										
48	2-Phenoxyethanol	122-99-6	4.2	0.0	29	1	69										
183	Tertiary butylphenol							<2.1	NR	NR	1	1					
184	Tetrachloroethene/Tetrachloroethylene/Perchlc	127-18-4	7.3	0.0	304	4	197	2.9	0.7	4.7	1	4	0.7	0.0	28	4	75
185	Tetradecane	629-59-4	2.5	0.0	13	1	69										
186	Tetrahydrofuran	109-99-9											4.5	NC	NC	3	26
187	Toluene	108-88-3	15	0.0	209	7	402	25	14	74	2	5	3.4	0.0	30	4	75
188	trans-1,2-Dichloroethene	156-60-5											0.0	0.0	0.4	2	24
189	trans-1,3-Dichloropropene	10061-02-6											0.0	0.0	0.0	2	24
190	Tributyl phosphate	126-73-8	1.0	0.0	6.4	1	69										
191	Trichloroethene	79-01-6	0.4	0.0	41	3	263	10	0.0	71	1	4	0.5	0.0	4.8	3	26
192	Tridecane	629-50-5	1.5	0.0	12	2	74										
193	Trichlorofluoromethane	75-69-4											0.2	0.0	6.0	3	71
194	Triethyl phosphate	78-40-0	0.4	0.0	18	1	69										
195	Trimethylpentylphenol	NO						<2.1	NR	NR	1	1					
196	Undecanal	112-44-7	1.4	0.1	5.2	1	69										
197	Undecane	1120-21-4	2.9	0.0	87	5	239						NC	0.0	20	1	49
198	Valeraldehyde	110-62-3	1.3	0.0	5.9	1	108						4.7	4.0	5.0	1	2
199	Vinyl acetate	108-05-4						NC	NC	NC	1	4	0.4	0.0	2.0	3	71
200	Vinyl Chloride	75-01-4											0.0	0.0	0.0	2	24
201	Xylene	1330-20-7	1.8	0.0	52	1	100										

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Status of database of measured contaminants:

2) New studies from 2019 are included. All substances in Yin et al. 2021 were already in Chen et al.

3) Cross check has been performed on data from reports of prior projects, including the EASA 2014 CAQ1 project

4) Data on additional VOCs and organophosphates reported in the CAQ1 project are now included.

Aware of other high quality measurement data from inflight conditions? Feel free to forward them to us.

Chen (All non-smoking flights) | **New Studies (Substances)** | New Studies (Particles)

Compounds	Chemical Abstract System (CAS) no.	Active sampling measurements (S6) Concentration(µg/m³) Avg.	Min.	Max.	Number of studies	flights	Pass… A…
Yin 2021: Cruising phase							
Formaldehyde	50-00-0	5,93	<LOD	20,03	1 Yin 2021	56*	
Acrolein & Acetone	107-02-8 and 67-64-1	20,68	<LOD	57,63	1 Yin 2021	56*	
Propionaldehyde	123-38-6	4	<LOD	29,52	1 Yin 2021	56*	
2-Butanone	78-93-3	8,3	<LOD	31,79	1 Yin 2021	56*	
Butyraldehyde	123-72-8	3,78	<LOD	33,54	1 Yin 2021	56*	
Benzaldehyde	100-52-7	2,37	<LOD	51,28	1 Yin 2021	56*	
Valeraldehyde	110-62-3	1,48	<LOD	39,71	1 Yin 2021	56*	
m&o-Tolualdehyde	620-23-5 and 529-20-4	1,13	<LOD	8,35	1 Yin 2021	56*	
Hexaldehyde	66-25-1	6,49	<LOD	47,75	1 Yin 2021	56*	
						* 28 short-hau	
Yin 2021 also has data on different aircraft age and data with or without carbon filters activated							

Chen (All non-smoking flights) | New Studies (Substances) | **New Studies (Particles)**

Substance measured	CAS number	Concentration(particle counts/cm³) Avg.	Min.	Max.	Number of studies	flights	Flight phase
Michaelis 2021: Different flight phases (Ultrafine particles)							
Ultrafine particles	n/a		35	96700	1 Michaeli	1	Peak occurred with associat
Ultrafine particles	n/a		76	31300	1 Michaeli	1	Peak immediately after eng
Ultrafine particles	n/a		147	81800	1 Michaeli	1	Peak occurred with associat
Ultrafine particles	n/a		893	97800	1 Michaeli	1	Peak immediately after eng
Also has information on particles in aricraft of different age							
Yu 2021: (Particle matter)							
PM1		0,47	0	9,31 µg/m3	1 Yu et al 2	4	Throughout all of the flight
PM2.5		0,91	0	12,37 µg/m3	1 Yu et al 2	4	Throughout all of the flight
PM10		1,14	0	15,36 µg/m3	1 Yu et al 2	4	Throughout all of the flight
CO2	124-38-9	1440 ppm	1069	2135 µg/m3	1 Yu et al 2	2	Only monitored in the seco
CO	630-08-0	0.07 ppm	0	0,26 µg/m3	1 Yu et al 2	2	Only monitored in the seco
Guan 2019: (Ultrafine particles)							
Ultrafine particles		72	almost same as averag	almost same as aver	1 Guan 20	14	Cruising
CO2	124-38-9	1100 ppm	739 ppmv	3374 ppmv	1 Guan 20	14	Cruising
Dominant peak (size) was 72-100 nm							
Some peak values were seen with turbulence of air stream or while passing through cloud							
There are also ultrafine particle counts during taxiing, climbing, descending and taxiiing (after landing)							
Rivera-Rios 2019: (Particle matter)							
PM1		~0	almost same as ave				
PM 0.3 to 2.5		~500	almost same as ave				
PM15		10 µg/cm3	almost same as ave				
Has also other phases of flying including at terminal, bording taxiing, climbing, descending, taxiing, deplaining,							

VOC substances in EASA 2014 that are not in Chen	CAS number	Mean in main study (µg/m3)	Mean in B787 study (µg/m3)
Naphthalene 16.8 1.4 0.0 49.1 0.4 2.6	91-20-3	1,4	0,8
p+m-Xylene 36.6 0.9 0.0 4.5 0.6 2.4	179601-23-1	1,6	0,9

Organophosphates in EASA 2014	CAS no	Mean in main study (µg/m3)	Mean in B787 study (µg/m3)	Already in Chen et al.?
Triisobytyl phosphate	126-71-6	0,102	0,016	no
Tributyl phosphate	126-73-8	0,43	0,237	Yes
Tris(chloroethyl)phosphate	115-96-8	0,016	0,007	no
Tris(chloroisopropyl)phosphate	13674-84-5	0,506	0,502	no
Tris(1,3-dichloroisopropyl)phosphate	13674-87-8	0,008	0,005	no
Triphenyl phosphate	115-86-6	0,009	0,006	no
Tris(butoxyethyl)phosphate	78-51-3	0,076	0,035	no
Diphenyl-2-ethylhexyl phosphate	1241-94-7	0,015	0,013	no
Tris(ethylhexyl)phosphate	78-42-2	0,004	<LOD	no
Tri-m-cresyl phosphate	563-04-2	0,004	0,007	no
Tri-mmp-cresyl phosphate T-mmp-CP	no cas	0,006	0,01	no
Tri-mpp-cresyl phosphate T-mpp-CP	no cas	0,004	0,006	no
Tri-p-cresyl phosphate	78-32-0	0,002	0,003	no

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WP1 FLOW and input from partners, scientific committe and stakeholders

→D4: Analysis of simulated CAC event tests and comparison with in-service reports and data

Task 1.1

Collect data on air cabin contaminants from existing datasets ("Baseline")

Task 5.1

Compare with compounds in project's fume events – which is increased?

Task 6.1a

For increased compounds, collect basic tox data to identify those of relevance for main symptoms reported

Point-of-departure:
Chen et al. 2021: Cabin air quality on non-smoking commercial flights;
additional searches;
stakeholder input

Compounds identified in oil related simulated fume events *(Fraunhofer)*

Identify main symptoms reported by aircrew personnel and passengers

CABIN AIR QUALITY III

Symptoms reported by aircrew personnel and passengers experiencing contaminated air in aircrafts

TABLE 2. STUDY B: INDEPENDENT MEDICAL FINDINGS/DIAGNOSES BY MEDICAL STAFF

SHORT-TERM MEDICAL FINDINGS & DIAGNOSES	No.	LONG-TERM MEDICAL FINDINGS & DIAGNOSES	No.
Hydrocarbon fume inhalation/chemical injury on aircraft	1	RADS (Reactive Airways Dysfunction Syndrome) / occupational asthma	6
Adverse effect on the vocal chords and bronchial tubes	1	PTSD (Post Traumatic Stress Disorder)	3
Tricresyl phosphate (TCP) in blood	1	Neurotoxic injury	1
Raised levels of VOCs, nickel, cell degradation	1	Toxic encephalopathy	1
Double hernia due vomiting	1	Neuropathy on vocal chords/limbs	3
Poisoning by non-medical agent	5	MCS (Multiple Chemical Sensitivity)	1
SPO2 70% / 80% (peripheral capillary oxygen saturation)	2	CFS (Chronic Fatigue Syndrome)	1
Abnormal blood results: CK; CK-MB; LDH; GOT (AST); GPT (ALT)	2	Anxiety/depression	1
Traumatic muscle damage and ischemia due excessive athletic sports or contamination	2	Cognitive dysfunction	4
Toxic effect of gas, fumes or smoke	2	Dementia	1
Possible inhibition of the enzyme AChe or other neurospecific esterase caused by organophosphates	2	ADHD (Attention Deficit Hyperactivity Disorder)	1
Toxicopy	2	Seizure disorder	1
carboxyhemoglobin at or above the high normal range - exposure to burned organic chemicals	4	Depression	1
TOCP (Triortho cresyl phosphate) adduct on Bche	1	Aerotoxic syndrome	1
Inhalation injury	1	Chemical injury at work	1
Organophosphate (OP) type poisoning/internal bleeding	1	Neurological chemical injury	1
		CNS injury	1
		G4 GBM (deceased) - (Glioblastoma brain tumour)	1
		Wallerian degeneration	1
		Vocal polyps	1
		Heart attack + phosphate exposure (deceased)	1
		Frontal lobe damage	1
		Optic nerve damage	1
		Migraines	1

Neurological symptoms marked in yellow

Michaelis et al. 2017, Public Health Panorama

CABIN AIR QUALITY III

Symptoms reported by aircrew personnel and passengers experiencing contaminated air in aircrafts

Table 4B Most often reported symptoms.

Symptoms	1[a]	2	3	4	5	6	7	8	9	10	11
Irritation of eyes, nose, throat	x	x	x	x	x	x	x	x			x
Salivation	x			x							
Nausea, vomiting	x	x	x	x	x		x	x	x	x	
Flu-like symptoms								x			
Headache	x	x	x	x	x	x	x	x	x	x	x
Fatigue	x	x	x		x	x		x	x	x	x
Lethargy							x				
Disorientation	x	x									
Dizziness	x	x	x	x	x	x	x	x		x	
Cognitive impairment			x		x	x	x	x		x	x
Memory impairment	x	x	x	x					x	x	
Confusion		x			x					x	
Balance/coordination loss	x	x	x	x	x		x		x		x
Tremor	x										
Irritability		x									
Blurred vision	x	x		x	x					x	
Breathing difficulties	x	x	x	x		x	x	x	x	x	x
Chemical hypersensitivity		x		x			x				
Chest pain	x										
Palpitations	x			x					x		x
GI-complaints, cramps			x	x		x	x	x			x
Diarrhea	x			x	x		x				
Loss of sensation, tingling		x	x		x		x		x		

[a]Study number see Table 3 A.

Observations that can be made in animal studies

Cage-side observation

Animal weight loss

Changes in behavior

Cage-side observation

Cage-side observation

Review. Hageman et al. 2022, Advances in Neurotoxicology

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WP1 FLOW and input from partners, scientific committe and stakeholders

→D4: Analysis of simulated CAC event tests and comparison with in-service reports and data

Task 1.1

Collect data on air cabin contaminants from existing datasets ("Baseline")

Task 5.1

Compare with compounds in project's fume events – which is increased?

Task 6.1a

For indicator compounds, collect basic tox data to identify compounds of interest for main symptoms reported

Select 20-30 compounds for more detailed assessment of toxicity related to symptoms reported by aircrew personnel and passengers

Point-of-departure:
Chen et al. 2021: Cabin air quality on non-smoking commercial flights;
additional searches;
stakeholder input

Compounds identified in oil related simulated fume events *(Fraunhofer)*

Identify main symptoms reported by aircrew personnel and passengers

Discussion
-Partners
-Scientific committee

CABIN AIR QUALITY III

For indicator compounds: collect basic toxicological data to identify compounds of interest for health effects

Is it probable that a substance might be relevant for observed symptoms?

1. - Measured level and duration of during simulated CAC event
   - Difference from “old” measurements during inflight conditions

2. - Level of knowledge on adverse health effects (especially neurotoxicity, covering many symptoms reported (based on extracts from the GESTIS information System)
   - Potency of toxicity (based on Occupational Exposure Limits)

WP1 FLOW and input from partners, scientific committe and stakeholders

→D4: Analysis of simulated CAC event tests and comparison with in-service reports and data

→D5: Report of toxicological analysis and tests performed

Task 1.1

Collect data on air cabin contaminants from existing datasets ("Baseline")

Point-of-departure: Chen et al. 2021: Cabin air quality on non-smoking commercial flights; additional searches; stakeholder input

Task 5.1

Compare with compounds in project's fume events – which is increased?

Compounds identified in oil related simulated fume events *(Fraunhofer)*

Task 6.1a

For indicator compounds, collect basic tox data to identify compounds of interest for main symptoms reported

Identify main symptoms reported

Select 20-30 compounds for more detailed assessment of toxicity related to symptoms reported by aircrew personnel and passengers

Discussion
-Partners
-Scientific committee

Task 6.1b

Collect detailed tox data for selected compounds

Task 6.2a

Analysis of retrieved data to identify hazard for selected health effects and knowledge gaps

(Neuro) Toxicological data from expermental studies (WP 3)

CABIN AIR QUALITY III

For selected compounds: collect and analyse toxicological data to identify hazards related to reported symptoms

Additional information retreived

- EU and World Health Organisation reports and databases
- Registry of Toxic Effects of Chemical Substances (RTECS)
- PubMed database if no high quality reports are identified
- Additional review reports via consortium partners and research projects
- In silico Quantitative Structure Activity Relationship (QSAR) screening for respiratory sesitisation in humans

Hazard identification and gap analyis of selected chemicals:

- Probable that the selected contaminants can induce relevant health effects?
- Gap in knowledge relative to the study of relevant effects

WP1 FLOW and input from partners, scientific committe and stakeholders

→D4: Analysis of simulated CAC event tests and comparison with in-service reports and data

→D5: Report of toxicological analysis and tests performed

→D8: Final report and recommendations

Task 1.1

Collect data on air cabin contaminants from existing datasets ("Baseline")

Point-of-departure: Chen et al. 2021: Cabin air quality on non-smoking commercial flights; additional searches; stakeholder input

Task 5.1

Compare with compounds in project's fume events – which is increased?

Compounds identified in oil related simulated fume events *(Fraunhofer)*

Task 6.1a

For indicator compounds, collect basic tox data to identify compounds of interest for main symptoms reported

Identify main symptoms reported

Select 20-30 compounds for more detailed assessment of toxicity related to symptoms reported by aircrew personnel and passengers

Discussion

-Partners

-Scientific committee

Task 6.1b

Collect detailed tox data for selected compounds

Task 6.2a

Analysis of retrieved data to identify hazard for selected health effects and knowledge gaps

(Neuro) Toxicological data from expermental studies (WP 3)

Task 6.2b

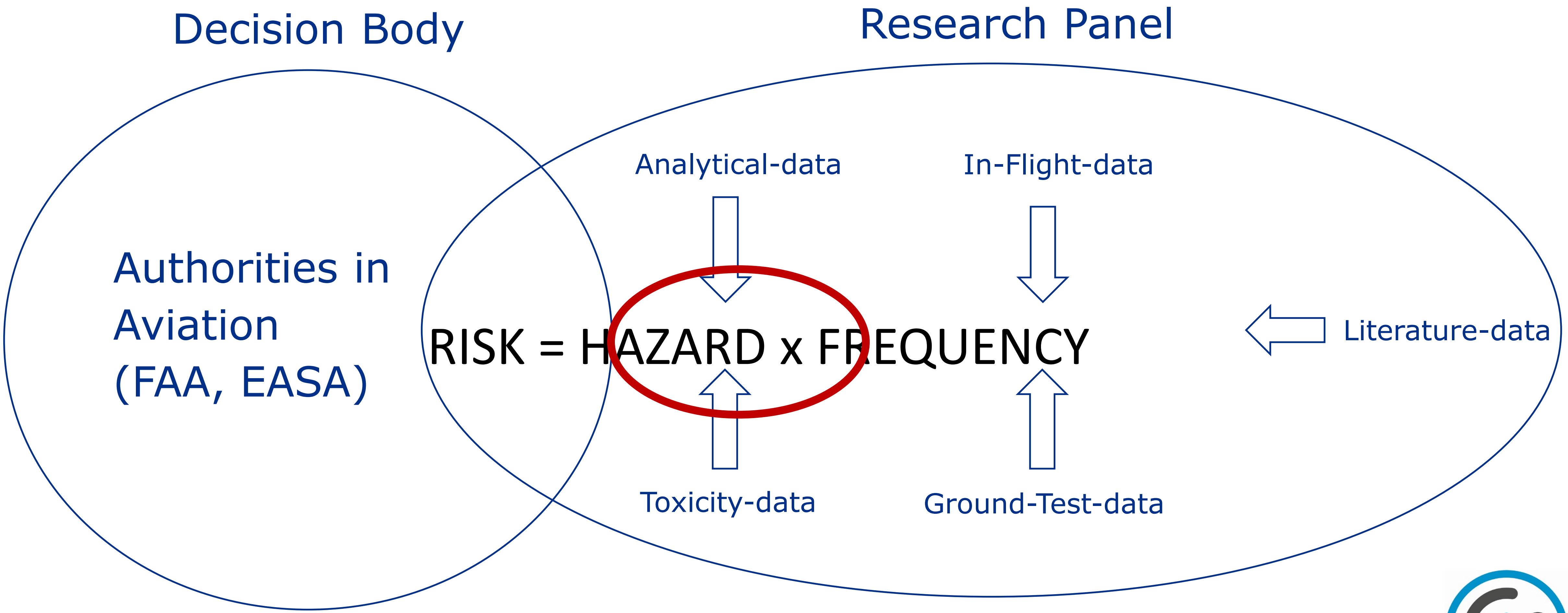
Develop recommend-actions for toxicological risk assessment (for a larger context and budget)

Input from partners

CABIN AIR QUALITY III

Why CAQIII?

Data Generation and analysis



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Thank you for your attention!

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GMC

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National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

HELMHOLTZ MUNICH

Fraunhofer IBP

National Research Centre for the Working Environment

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National Research Centre for the Working Environment

FFIKA, Focused Research Effort on Chemicals in the Working Environment in Denmark

Basis: Haber's rule

Haber 1924:

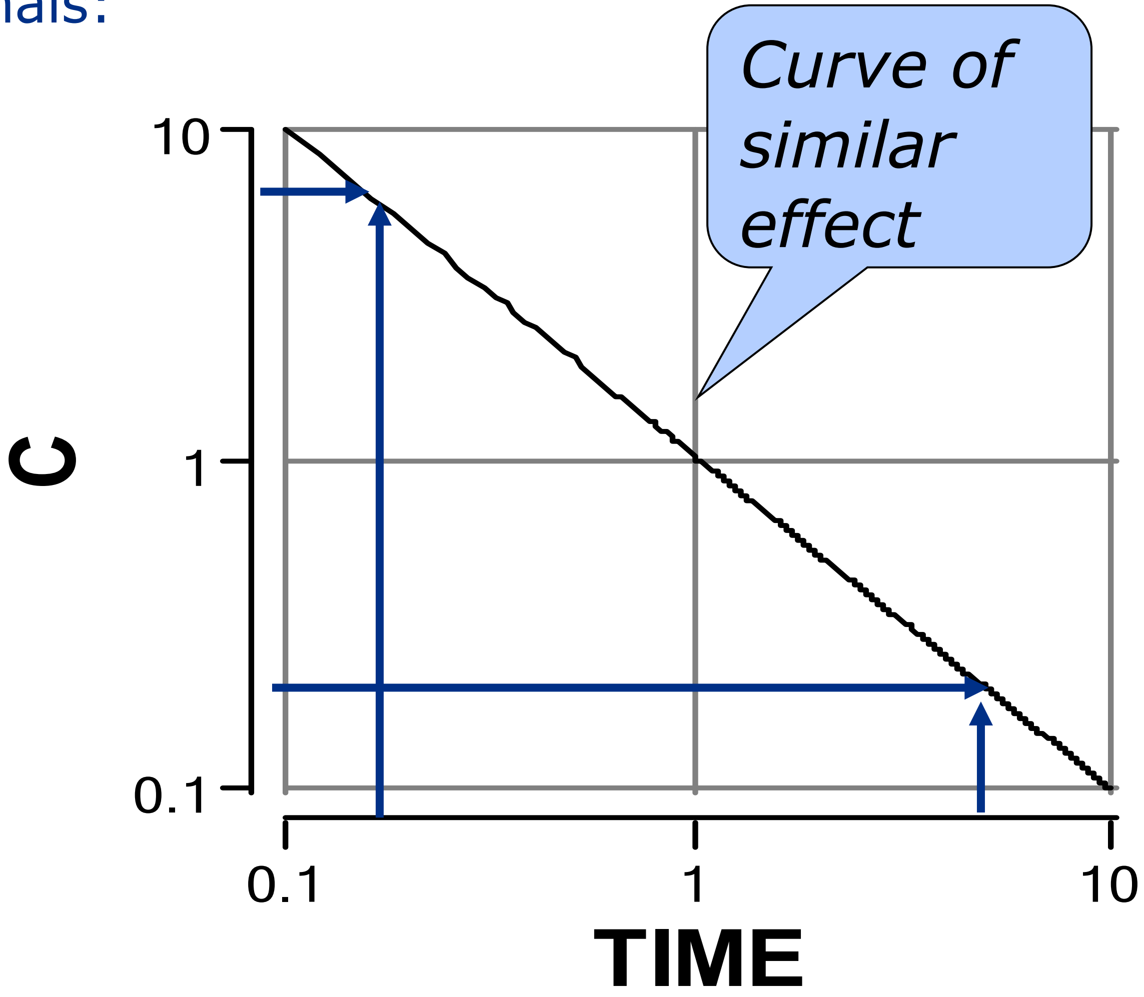
Constant relation between concentration of war gases and time to death of test animals:

Effect of short exposure to high concentration

=

Effect of long exposure to low concentration

Average exposure (and not peaks) matters



for the Working Environment

Task 6.2b: Development of recommendations for future toxicological risk assessment

- Problem formulation:
  - Setting
  - Methodology relative to exposure to multiple chemicals
- Exposure assessment
- Hazard assessment and characterisation
  - Additional knowledge (studies) needed?
- Risk characterisation