Benzene

Proposed Occupational Exposure Limit

Petroleum Safety Authority Norway

26 October 2018

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Chairman of the ECHA Committee for Risk Assessment

ECHA Committee for Risk Assessment RAC

- Members are nominated by the EU/EEA Member States but appointed by the Management Board of ECHA in their personal capacity as scientists
- 56 members currently, including 5 co-opted and 2 EEA members from Norway
- Chaired by a staff member of the agency
- Consensus body with voting rules
- Meets 4 times per year for up to two weeks and adopts ca, 100 opinions per year
- RAC is responsible for providing opinions to the European Commission on:
  - EU-wide Restrictions,
  - Applications for Authorisation of continued use of SVHCs in the workplace
  - Harmonised Classification & Labelling
  - Occupational Exposure Limits (as part of a COM pilot project since 2017)

Occupational Exposure Limit methodology

Mode of Action-based thresholds

- Genotoxic carcinogens usually considered not to have a threshold
- Can act through complex (multiple) modes of action
- Some critical mode(s) of action may contain key steps with thresholds
- Identifying such steps is one thing but determining a threshold can be challenging
- Only where such thresholds are well supported scientifically, can they be used to determine limit values
- For a health-based limit, remaining cancer risk should be 'negligible'
- Where the data is insufficient, a non-threshold approach is always taken

RAC Benzene OEL Opinion

Commission mandate (March 2017) to ECHA under the Carcinogens and Mutagens Directive

- By 29 May 2017, RAC to provide an evaluation of OELs for arsenic acid and its salts – As(V) and 4,4'-methylene-bis(2-chloroaniline) – MOCA for the 3rd amendment to CMD
- By 30 March 2018, RAC to provide an evaluation of OELs for **benzene**, acrylonitrile and nickel and its compounds

ECHA drafted the reports and RAC evaluated the proposed OELs, providing an opinion. The amended reports are provided as background documents

CLP Classifications for benzene

Annex VI of CLP hazard class and category	Hazard statement code
Flam. Liq. 2	H225
Skin Irrit. 2	H315
Eye Irrit. 2	H319
Asp. Tox. 1	H304
Muta. 1B (may cause genetic defects)	H340
Carc. 1A (may cause cancer)	H350
STOT RE 1	H372

Current OEL for benzene

- Scientific Committee on Occupational Exposure Limits (SCOEL, 1991/2006)
  - 8 hour Time Weighted Average **<1.0 ppm** (< 3.25 mg/m^3); „skin" notation
  - Biological limit values for benzene
    - S-phenylmercaturic acid in urine
    - *trans*,*trans*-muconic acid in urine
- Directive 2004/37/EC, Annex III (2004)
  - Limit value of 1 ppm (3.25 mg/m^3); „skin" notation

Recent evaluations of benzene

- The Netherlands / DECOS (2014)
  - OEL 0.2 ppm; threshold approach based on haematological effects in workers
- Germany / AGS (2012)
  - Linear risk extrapolation; based on an ED10 of 15 ppm for leukaemia from all available cohorts

Benzene air (ppm)	Benzene air (mg/m^3)	Risk
0.6	1.9	4 : 1,000
0.06	0.2	4 : 10,000
0.006	0.02	4 : 100,000

- Many other reviews considered by RAC: SCOEL 1991; ATSDR 2007, 2015; IARC 2012; ANSES 2014; Concawe 1999, 2002, 2006, 2012; EU-RAR, 2008

Mode of Action for benzene

- Haematological effects
  - haematological suppression affecting all blood cell types
- Immunological effects
  - e.g., immunosuppression
- Genotoxic effects
  - clastogenic (chromosom breakage) and aneugenic (chromosome numbers) effects
  - oxidative damage
  - mutagenic effects secondary
- Carcinogenic effects
  - leukaemia in workers

Conclusions of the evaluation 1

- Extensive human database - epidemiological studies of workers generally consistent: excess cancer risk, in particular acute myeloid leukaemia (affecting bone marrow progenitor cells)
- Various studies show induction of adverse chromosomal damage in benzene-exposed workers from different working environments
- Primary DNA reactivity of benzene and/or its metabolites of lesser importance
- The leading genotoxic effects, aneugenicity and clastogenicity, are considered to be of a secondary nature, i.e. acting indirectly and to follow a non-linear threshold-mechanism

Conclusions of the evaluation 2

- The metabolism of benzene is inherently complex: oxidation to benzene oxide by cytochrome P-450, mainly CYP2E1, then numerous reactive/toxic metabolites, ROS are formed via several pathways
- It is assumed that benzene will also be metabolised directly in the bone marrow to toxic metabolites with accompanied redox cycling and reactive radical formation
- The major and most sensitive target organs of benzene are the bone marrow and the haematological system

Conclusions of the evaluation 3

- A mode-of-action-based threshold for chromosomal damage (aneugenicity and clastogenicity) in workers can be used to establish an OEL for carcinogenicity

- The limit so derived, will:
  - avoid exposures that induce chromosomal damage in workers,
  - will also avoid other adverse effects, e.g. will also avoid exposure causing haematological suppression

Genotoxic effects

Weight-of-evidence approach to the broad body of human data

- LOAEL in the range of 1 ppm and above
- Questionable/borderline effects in the range of 0.5 ppm
- Indications for NOAEL in the range of 0.1 ppm
- Uncertainty needs to be adequately taken into account

Genotoxicity – data (Europe)

BZ ppm	CA	MN	N (E/C)	Comment	Reference
2.2 max 15	+		42/42	Matched for age and smoking; max. 15 ppm	Major et al 1994
0.46 ±0.14	(+) p=0.066	—	23/24	CBMN; only non-smokers; 22 y expo; MN correlates with age	Carere et al 1995
0.28 ±0.04		—	50/43	Smokers: 66/40% Age: 43/40 a	Pitarque et al 1996
0.10 ±0.01		—	12/12	CBMN/FISH; matched for age and smoking	Carere et al 1998
0.10 ±0.10	—	(+?)	19/31	Mean CBMN correlates with age and BZ (no BZ effect on median MN or range)	Lovreglio et al 2014
0.1	**NOAEL**				
0.07		—	21/19	MN correlates with age and smoking	Bukvic et al 1998
0.03 ±0.03		—	79/50	CBMN correlates with age and smoking	Basso et al 2011
0.01 max 0.8	—		19/16	Smokers: 42/56%	Fracasso et al 2010

Genotoxicity – data (Asia)

BZ ppm	CA	Aneugen	MN	N (E/C)	Comment	Reference
5.0±3.6		+		47/27	Shoe factory Tianjin	Zhang et al 2011
2.6±2.7		+		28/14	Shoe factory Tianjin	Zhang et al 2012
2.3±1.4	+			130/51	Shoe factory Tianjin	Qu et al 2003a
1.0±2.6	+ (sperm)			30/11	Shoe factory Tianjin	Marchetti et al 2012
1.0±2.6		+(sperm) — (PBL)		17/33 17/17	Shoe factory Tianjin	Xing et al 2010 Ji et al 2012
1.0		**LOAEL**				
0.56 (0.1-0.74)	+	+		82/76	Coke oven workers, Korea (PAH expo); more smokers; prev. expo. higher?	Kim et al 2004
0.51; max. 4.3	+	+	+	108/33 30/10	Petroleum refinery workers, Korea, only stationary exp. measurements, exp. up to 4.3 ppm	Kim et al 2008 Kim et al 2010
0.06 ±0.01			—	132+129 /130	CBMN, decorators, painters, masks used	Sha et al 2014

OEL derivation – dealing wit remaining uncertainty

LOAEL 1 ppm

- Assessment factors applied:
  - 2 for intraspecies variability
    - less robust data below 1 ppm
    - polymorphisms
  - 10 for dose-response
    - LOAEL to NOAEL
    - bone marrow may exhibit higher sensitivity
    - severity of endpoint

OEL 0.05 ppm

- This limit is considered to have no significant residual cancer risk

RAC proposal: OEL for benzene

OEL as 8-hour TWA	**0.05 ppm (0.16 mg/m³)**
STEL	**Not established**
BLV	0.7 µg benzene/L urine 2 µg S-phenylmercapturic acid (SPMA)/g creatinine (sampling: end of exposure or end of working shift)
BGV	0.3 µg benzene/L urine 0.5 µg S-phenylmercapturic acid (SPMA)/g creatinine
Notation	**skin**

Exposure and analytical feasibility

Benzene exposure

Between 0.05 and 0.1 ppm	Above 0.1 ppm
Landscaping work (GM 0.003 ppm, maximum 0.06 ppm; Breuer *et al* 2015)	**Gasoline pump calibration** (AM 0.13 ppm, maximum 0.28 ppm; Concawe 2009)
Service station workers - Italy, (AM 0.02 ppm, maximum 0.09 ppm; Campo *et al* 2016)	**Gasoline pump repair and maintenance** (AM 0.25 ppm, max 0.89 ppm; Concawe 2009)
Petrochemical industry (average <0.05 ppm, maximum 0.28 ppm; Carrieri *et al* 2012; Breuer *et al* 2013)	**Maintenance and shut down in refineries** (mean 0.06-0.3 ppm, maximum 1.4 ppm; Akerstrom *et al* 2016)
R&D laboratories (AM 0.05 ppm, maximum 0.2 ppm; Concawe 2009)	**Repair shop** for gasoline-powered gardening tools (AM 0.4 ppm; Breuer *et al* 2013)
Service station workers - Spain (AM 0.05 ppm, GM 0.04 ppm, maximum 0.17 ppm; Periago and Prado 2005)	**Simulation experiment** - short term use (30 min) of lacquer spiked - 0.05% benzene (0.91 ppm; HVBG 2001)
Fuel tank drivers (AM 0.09 ppm, maximum 0.3 ppm; Lovreglio *et al* 2014, 2016	**Tank cleaning** - upstream petroleum industry (AM 1.4 ppm, GM 0.3 ppm, maximum 16.8 ppm; Kirkeleit *et al* 2006)
Repair workshops (GM 0.10 ppm, maximum 0.4 ppm; Breuer *et al* 2013).	

Occupational Exposure reviews

Table 7: Overview of occupational exposures to benzene in Europe (and USA; extract)

Work area / Occupation	N	Average (mg/m^3)	Range (mg/m^3)
Refineries	540	0.005-**3.7**	0.002-8.3
Chemical industry	351	0.003-0.035	<0.001-0.9
Coke oven industry	57	0.12-1.2	Max 24
Tank filling/ tank drivers	109	0.2-0.6	0.002-1.2
Service stations / Repairing workshops	122	0.02-0.24	0.001-2.9
Traffic / Use of gasoline-engined equipment	204		<0.002-0.2
Use of gasoline-derived products	465	0.00003-**3.2**	Max 9.1

Conclusion on workplace exposure

- At workplaces in Europe, the long-term average exposures to benzene are mainly below 0.1 ppm (0.3 mg/m^3) and even below 0.05 ppm (0.16 mg/m^3).
- However, higher exposures have been reported for several diverse groups.

Analytical methods for benzene

Several methods can fulfil the requirements:

- **Active sampling:** three methods can achieve less than 10% of the OEL in 8 hours or less.
  - **IFA 6265** : can measure 1% of the OEL in 1 hour
  - **ISO 16000-6**: can measure 2% of the OEL in 2 hours
  - **OSHA method 1005**: 10% of the OEL in less than 4 hours (and could be extended to 8 hours sampling time - OSHA tested this
- **Passive sampling** ISO 16017-1
  - **OSHA Method 1005:** Can also measure 0.1 of the OEL

Notes: Thermal desorption (IFA and ISO) has been used for many years and is routine nowadays (so equipment is available in most labs). There is also a chemical desorption method available (OSHA) that can reach 10% of the OEL

Next steps

Setting of OELs for carcinogens at EU level follows the ordinary legislative procedure

(For Indicative OELs a lighter legislative procedure applies)

1

Selection of chemicals for Scientific Evaluation

DG EMPL establishes lists of priorities for scientific evaluation based on inputs from various sources and application of priority criteria.

2

Scientific Recommendation

DG EMPL issues mandates to scientific committee, who will deliver as a rule the **exposure-risk-relationships (ERR)** for non-threshold carcinogens, or **a practical threshold when possible**. Scientific Recommendations are subject to external consultation before adoption.

3*

WPC - ACSH

The Working Party on Chemicals (WPC) discusses the scientific Recommendation and various feasibility issues and comes up with a consensus based suggestion for the OEL value. This is integrated in a draft opinion for adoption by the Plenary of ACSH.

4

Impact Assessment (IA)

DG EMPL drafts IA containing policy options and associated impacts. IA is discussed within an Interservice Steering Group and submitted to the Regulatory Scrutiny Board (RSB). A positive reply is required.

5

Draft legislative proposal

DG EMPL prepares the draft legislative proposal and submits it to inter-service consultation. Thereafter, a final draft legislative proposal is prepared.

6

College of Commissioners

The College of Commissioners adopts the proposal and sends it to Council and Parliament for negotiation and subsequent adoption. As a Directive.

7

Adopted Directive published in EU Official Journal

MSs will transpose the legal text into national legislation by the date set in the Directive.

The procedure for indicative OELs is simpler, i.e. by Commission Decision

*2 stages of social partners' consultation have to be carried out in accordance with article 154 of TFEU

Next steps

- For benzene, a binding OEL under the Carcinogens & Mutagens Directive is proposed (part of the 4th amendment)
- At present the study that will support the Commission Impact Assessment is ongoing
- DG-EMPL aims to conclude the draft Advisory Committee on Safety and Health Opinion in the meetings of the Working Party on Chemicals in 2019
- Formal adoption of the Opinions by the ACSH plenary is anticipated later in the year

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Thank you for your attention

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