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A sector group of Cefic
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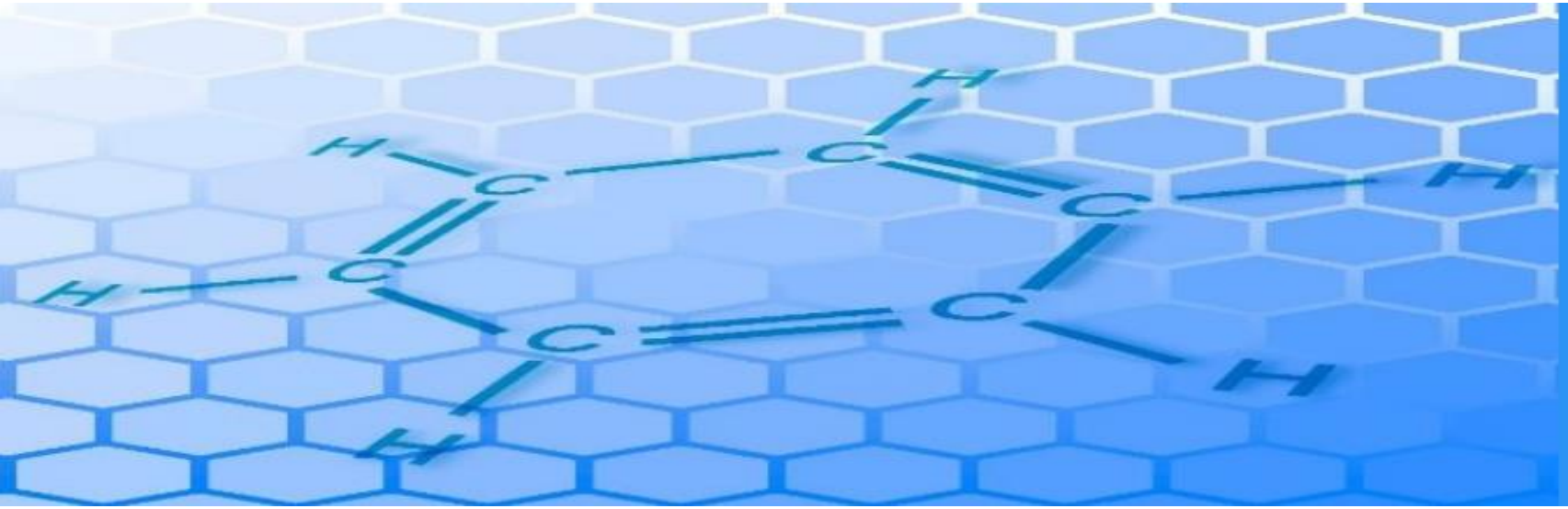
RAC Opinion on a Benzene OEL (2018) Background and Key Facts

Peter J. Boogaard



APA Symposium
Helsinki, Finland
11 September 2019

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CONFLICTS OF INTEREST

Shell International, Shell Health:
Global Discipline Leader & Manager Toxicology

Wageningen University, Division of Toxicology:
Professor of Environmental Health & Human Biomonitoring

Health Council of The Netherlands, serving on:
- Committee on the Evaluation of Carcinogens
- Dutch Expert Committee on Occupational Standards (DECOS)

Scientific Committee on Occupational Exposure Limits (SCOEL)

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CLARIFICATION

- Symposium organizers had invited ECHA-RAC to provide a speaker. Unfortunately, due to 50th RAC meeting, no speaker was available.
- As the RAC Opinion is a key part of the regulatory perspective for benzene in the EU, the symposium organizing committee felt it was important to include a brief on the RAC Opinion
- The following brief is derived from Public Information relating to the RAC OEL Opinion including an ECHA Presentation to The Norwegian Oil Industry Association.
- This presentation should not be taken as being a representation of ECHA-RAC views nor a comment on the RAC Opinion: It is just a presentation of key facts to set the scene.

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RAC BENZENE OEL OPINION - BACKGROUND

- EU Commission had decided that ECHA-RAC should provide health assessments to DG EMPL for the OEL setting process rather than SCOEL
- Joint RAC-SCOEL Joint Task Force (2015-2017) worked to agree technical approaches including use of mode of action
  - "The methodology and underlying principles for establishing MoA based thresholds are appropriate and feasible for use under REACH with some adaptation [and under CMD]"
- May 2017 – COM Mandate to RAC to provide OEL Opinions for Benzene (plus 4 other substances) → Benzene Opinion required for 26 March 2018 latest.
- Now (in retrospect) recognised that :
  - This was an challenging time scale for a complex data rich substance
  - 1 month Public Consultation on draft in October 2017 was too short → Commitment now to longer Consultation periods
  - ECHA-RAC lacks specific expertise to derive OELs → now dedicated experts added to RAC

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RAC FINAL OPINION ON BENZENE OEL – ADOPTED 9 MARCH 2018

- Draft at October 2017 Public Consultation considered a non-cancer health limit based on haematotoxicity and immunotoxicity data could drive an OEL of 0.1 ppm (8-h TWA).
- Varying cancer risk estimations presented but AGS 2012 risk estimate preferred (at 6.7 x 10^{-3} per ppm)
- Final RAC Opinion 9 March 2018:
  - OEL (8h TWA) : 0.05 ppm (0.16 mg/m^3)
  - STEL : Not Established
  - BLV : 0.7 µg benzene/L urine
  - 2 µg S-phenylmercapturic acid (SPMA) /g creatinine
  - (sampling: end of exposure or end working shift)
  - BGV : 0.3 µg benzene/L urine
  - 0.5 µg SPMA/g creatinine
  - Notation : Skin

RAC CONSIDERATIONS

MoA for benzene:

- **Immunological effects** (immunosuppression)
- **Haematological effects** (suppression of all blood cell types)
- **Genotoxic effects** (focus on clastogenicity and aneuploidy)
  - Clastogenicity, aneuploidy
  - Oxidative damage
  - Secondary mutagenic effects

→ **Carcinogenicity** (leukemia)

CONCLUSIONS OF THE EVALUATION (1)

- Extensive human database – epidemiological studies in workers usually consistent: excess leukemia (AML) via damaged bone marrow progenitor cells
- Several studies show induction of chromosomal damage in benzene-exposed workers in different working environments
- Primary DNA-reactivity of benzene or its metabolites seems of less importance (→ absent)
- The leading genotoxic effects, clastogenicity and aneugenicity, are of secondary nature, i.e. acting indirectly and following a non-linear threshold mechanism

CONCLUSIONS OF THE EVALUATION (2)

- The metabolism of benzene is inherently complex with ROS formation via several pathways
- Benzene is assumed to also be directly oxidised in the bone marrow to toxic metabolites, with redox cycling and reactive radical formation
- The major and most sensitive target organs of benzene are the bone marrow and the haematological system

→ At second instance haematological effects were used as the basis to derive an OEL

→ The underlying idea: if you prevent haematological effects you prevent the possible subsequent effects (similar to DECOS, 2014)

HAEMATOLOGICAL EFFECTS

- Huge database available with investigations of large numbers of benzene-exposed workers for haematological effects
- All studies show some shortcomings(s): no study controlled for co-exposure to other chemicals
- Mainly recent studies reviewed (≥ 2000)
- A weight-of-evidence approach was followed:
  - LOAEL in the range of 2 ppm
  - NOAEL in the range of 0.5 ppm

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Haematological effects as an endpoint

BZ ppm	Result	N	Exposure measurements	Haematology	Reference
2.6	+	10,702	personal and stationary	Several param.	Koh et al 2015
2.3	+	130	personal	Several param.	Qu et al 2003a
>2	+	250	personal	Several param.	Lan et al 2004
2.0	+	385	personal	Only WBC	Ye et al 2015
2.0	**LOAEL**				
1.7	—	153	personal	Several param.	Pesatori et al 2009
1.6	+	317	personal	Only WBC	Zhang et al 2016
0.7	—	121	stationary	Several param.	Huang et al 2014
0.6	—	1200	repres. personal	Several param.	Tsai et al 2004
0.6	—	387	personal	Only lymphopenia	Collins et al 1997
0.5	**NOAEL**				
0.4	BMDL (5%)			Reduced neutrophils	LOA 2017 (Qu et al 2003a)
0.3	—	61	personal	Several param.	Kang et al 2005
0.2	—	701	stationary	Several param.	Swaen et al 2010
0.1	—	200	stationary	Several param.	Collins et al 1991

GENOTOXIC EFFECTS

- Benzene induces MN, CA, aneuploidy, SCE, and strand breaks
- Leading are clastogenicity and aneuploidy
- Little/minor role for primary DNA reactivity:
  - Negligible binding of benzene to DNA (^{32}P-postlabelling at carcinogenic doses in rat)
  - No benzene oxide DNA adducts in mice or humans
- Possible genotoxic mechanisms:
  - Redox cycling and ROS formation: indirect DNA damage
  - DS breaks (ROS ?), appear important in benzene toxicity as their repair may be highly error prone
  - Aneuploidy may result from reactins with protein
  - Indirect mechanisms for DNA mutations (oxidative damage, error prone DNA repair)

AVAILABLE GENOTOXICITY DATA

- Mainly human data considered
- Studies investigating clastogenic or aneugenic effects only in a limited number of workers
- All studies have some shortcoming(s)
- No study controlled for co-exposure to other chemicals, however, there are not so many chemicals in the workplace leading to aneugenic effects
- Not considered:
  - Comet assay: inconsistent results; relevant co-exposures, methodological differences
  - Traffic personnel: co-exposure to complex mixture of traffic exhausts and low exposure to benzene
  - Fuel filling attendants in Asia: proven or assumed bad working conditions

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Genotoxicity effects as an endpoint (1)

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

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Genotoxicity effects as an endpoint (2)

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

BASIS FOR RAC OPINION ON BENZENE OEL

Overall data:

- Haematological effects (suppression of all cell types)

- LOAEL in the range of 2 ppm
- NOAEL in range of 0.5 ppm

- Genotoxic effects (focus on clastogenicity and aneuploidy)

- LOAEL in range of 1 ppm and above
- Questionable/borderline effects in range of 0.5 ppm
- Indications that NOAEL is around 0.1 ppm

Weight of evidence

→ but uncertainties need to be adequately addressed

DERIVATION OF OEL:

Overall LOAEL taken as being 1 ppm

- Assessment Factors used:
  - Intraspecific variability = 2
    - data less robust below 1 ppm; consideration of polymorphisms
  - Dose Response = 5 × 2
    - LOAEL → NOAEL, severity of endpoint; bone marrow may be more sensitive
- OEL Derivation:
  - 1 ppm / (2 × 5 × 2) = 0.05 ppm (as 8-h TWA)
  - This limit is considered to have no significant residual cancer risk

Thank you … for your attention !