Lower Olefins and Aromatics Reach Consortium (LOA)

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DEVELOPING A BENZENE OEL USING STUDY QUALITY ASSESSMENT TOOLS

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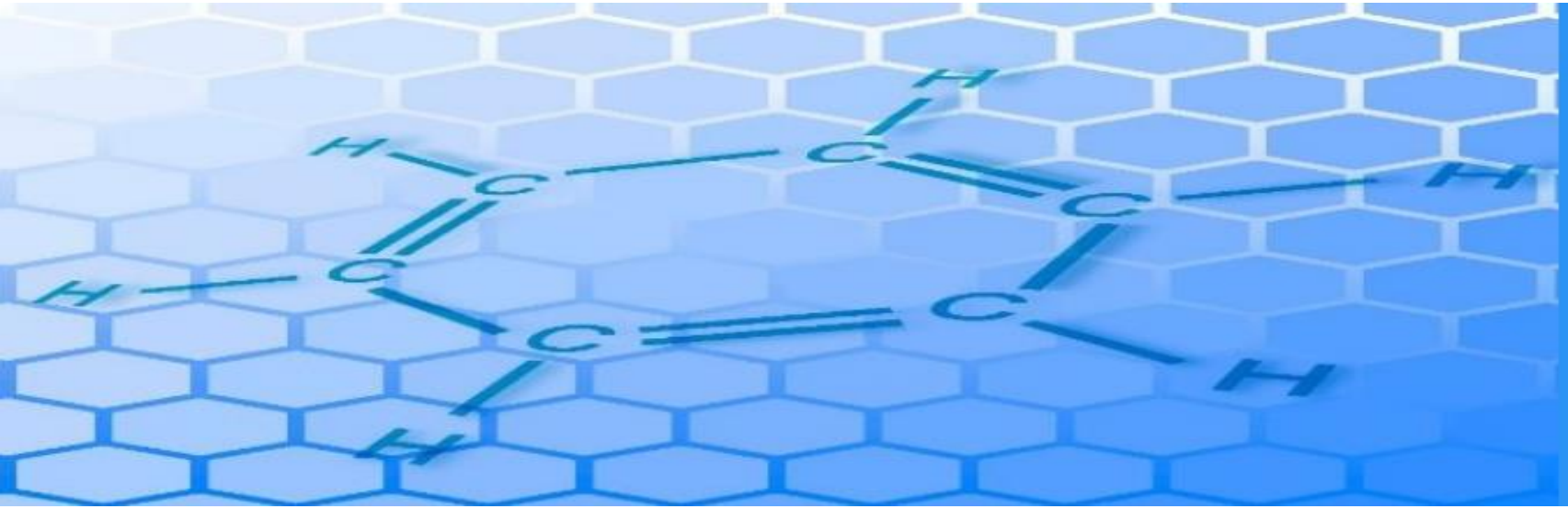
On behalf of the LOA Benzene Working Group



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BENZENE HEALTH EFFECTS LITERATURE

- Presentation is a preliminary communication of the group's work. A publication is in preparation and will be submitted for publication this year.

- Benzene is a known human carcinogen, more definitively linked to AML
- Genotoxic effects: Aneuploidy, clastogenicity
  - Weight of evidence indicates not a direct-acting mutagen
- Haematotoxic effects: decreased blood cell counts, pancytopenia, aplastic anemia
  - High exposures → more severe effects (aplastic anemia)
  - No clear consensus on cell-type specific effects e.g. neutropenia, lymphopenia
- Immunologic effects are known to exist; fewer studies
- Recent focus has been genotoxicity (ECHA), haematotoxicity (DECOS)

WHY IS QUALITY ASSESSMENT REQUIRED?

- Benzene literature is voluminous and diverse
  - Types of studies and quality vary markedly
- Structured tools exist for experimental studies (e.g. Klimisch et al 1997)
- Sanderson et al (2007) reviewed 86 tools to assess quality and bias in observational epidemiology studies.
- Exposure assessment is usually a 'weak link' in epidemiologic studies
- Quality Assessment Tools that emphasize exposure assessment are needed
  - Vlaanderen et al (2008) was selected as the most appropriate tool:
    - Exposure measurement quality parameters
    - Suitability of studies for risk assessment

MODE OF ACTION FOR CARCINOGENESIS - RATIONALE

- Evaluated weight of evidence for direct-acting mutagen and immune-mediated cycles of depletion/proliferation
  - Weight of evidence favours immune-mediated MOA
  - Consequences of immune-mediated MOA may include indirectly increasing (epi)genetic instability of cells
  - Immune-mediated MOA leads to threshold expectation
- Early key events in immune-mediated MOA include genotoxicity and haematotoxicity
  - Protecting against early key events is anticipated to protect from carcinogenicity
- Thus, focus on genotoxicity and haematotoxicity as biomarkers of risk from exposure.
- Human studies (not in vitro or animal) – Many studies in the relevant species

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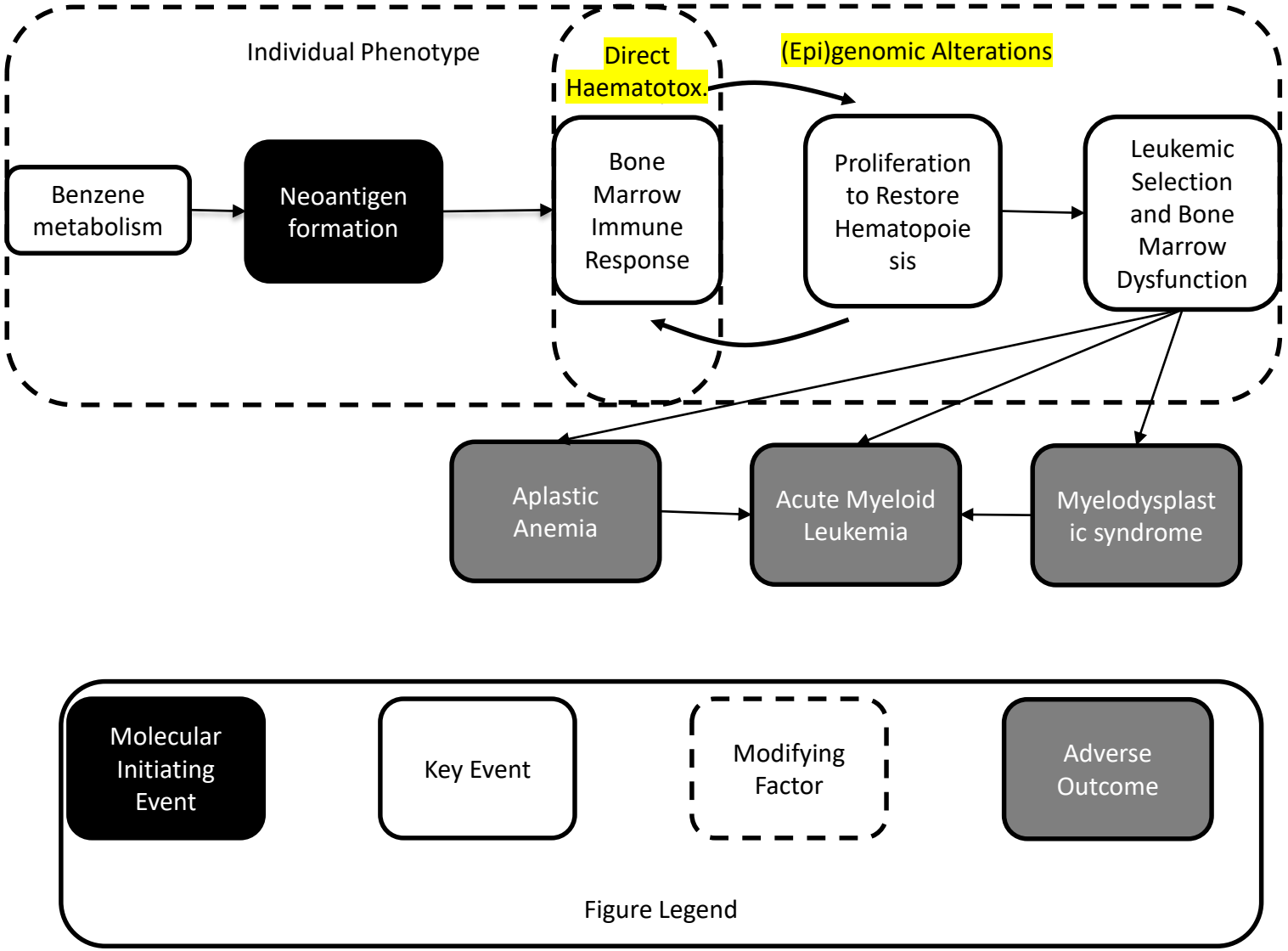
MODE-OF-ACTION HYPOTHESIS FOR BENZENE-INDUCED CARCINOGENESIS



PROJECT DEVELOPMENT

- Identify relevant literature (Haematotoxicity, Genotoxicity)
- Screen out unusable studies
- Score and rank studies by consensus quality score
- Derive Low Observed Adverse Effect Levels (LOAECs) and No Observed Adverse Effect Levels (NOAECs) where possible for the high quality studies
- Determine if LOAECs/NOAECs are certain or less certain
- Review LOAECs/NOAECs to derive an OEL
- Sensitivity analyses to check validity of proposed OEL

HAEMATOTOXICITY, GENOTOXICITY STUDIES ON BENZENE

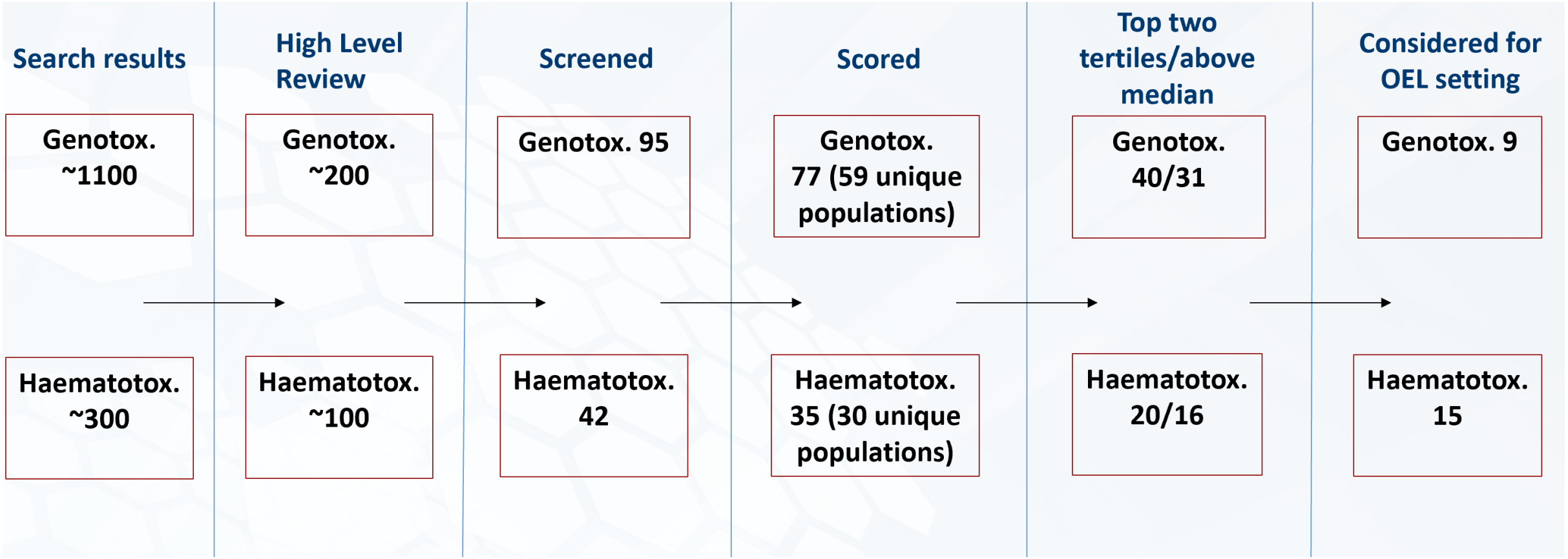
Literature review results (including references cited by IARC 2018)

- Genotoxicity- Sep 2018 - over 1000 studies
- Haematotoxicity – Nov 2018 – about 300 studies

Screening criteria – must pass initial screen to be accepted for quality scoring

- Study design (cohort, case-control, cross sectional)
- Benzene was specifically measured (not ”solvents”, “aromatics”, etc.)
- Benzene measured on ratio scale (true zero, not ratings/rankings)
- Statistical analysis present and described adequately
- Subject inclusion criteria present and described adequately
- Health outcome assessed via recognized norms
  - For genotoxicity, focused on aneuploidy, chromosome aberrations (- gaps), and micronuclei
- Confounders considered
- **After screening, 77 genotoxicity and 35 haematotoxicity studies were scored**

LITERATURE SEARCH REVIEW SUMMARY



SCREENING CRITERIA AND EXAMPLES OF EXCLUDED STUDIES

Must pass initial screen to be accepted for quality scoring

- Study design (cohort, case-control, cross sectional)
- Benzene was specifically measured (not ”solvents”, “aromatics”, etc)
- Benzene measured on ratio scale (true zero, not ratings/rankings)
- Statistical analysis present and “described in detail”
- Subject inclusion criteria present and “described in detail”
- Health outcome assessed via recognized norms
- Confounders considered

- Jamebozorgi et al 2016; Martino-Roth et al 2003; Kasuba et al 2000; Goncalves et al 2016
  - No ratio scale benzene data
- Pitarque et al 1999, Brogger et al 1990
  - Non-specific exposure measurement (aromatics, solvents, gasoline, etc)

QUALITY ASSESSMENT CRITERIA/SCORING

- Based on Vlaanderen, but modifications were necessary due to the following:
  - Nearly all studies were cross-sectional
  - More recent exposure preferred (weeks/months versus years/decades)
  - Individual exposure measurement for each subject was often feasible
  - Biomarkers of internal exposure often supplemented air readings
- Specific changes to Vlaanderen:
  - Operationalized: strength of statistical analysis, confounder control, information bias, sensitivity analysis for LOAEL/NOAEL assessment
  - Added a criterion for precision/power
  - Operationalized confounder control (for genotoxicity and haematotoxicity)

SCORING CRITERIA

EA criteria	Scoring
Methods	0, 0.5, 1
Variability	0, 0.5, 1
Application	0, 0.5, 1
Metric	0, 0.5, 1
Specificity	0, 0.5, 1
Quality	0, 0.5, 1
Blinding	0, 0.5, 1
Total	**0-7**

Other criteria	Scoring
Statistical Analysis	0, 1, 2, 3, 4, 5
Confounding	0, 0.5, 1, 2, 3
Information bias	0, 1, 2, 3
Sensitivity analyses	0, 1, 2
Power and precision	0, 1, 2
Blinded outcome	0, 1, 2
Total	**0-17**

Total possible score: 24 **Range of final scores: 6-20**

RANKING OF EXPOSURE CONTEXT AND ENDPOINT DATA FOR GENOTOX.

- Exposure context – can effects be ascribed to benzene per se:
  1. Factory – most likely (most pure exposure)
  2. Fuel – compromised by exposure to motor vehicles exhausts (PAHs), dermal
  3. Ambient Air – least likely (background levels of benzene, VOC's, diesel particulates, etc.)
- Genotoxicity endpoint: analysis based on endpoints more likely to be relevant and adverse due to MOA hypothesis:
  - Chromosome aberrations (minus gaps)
  - Micronuclei
  - Aneuploidy

CONSENSUS SCORING

- Developed detailed instructions on scoring
- Piloted understanding of instructions (2x) on two sets of studies, recalibrated instructions to improve clarity and based on feedback
- Experts in epidemiology, statistics, toxicology, exposure assessment screened and scored each study independently
- Individual scores were discussed in face-to-face meetings and by telecon
- Consensus scores developed for each study

EXAMPLE 1 - HIGH SCORING STUDY, CERTAIN LOAEL (1)

- Three papers by Xing et al (2010)(Ji et al (2012) and Marchetti et al (2012)) examined aneuploidy and chromosomal aberrations of chromosomes 1, 21, X and Y in sperm from the same population of 33 men exposed to benzene within 3 Chinese factories making shoes, paper bags and sandpaper.
- Group of studies assigned high score of 19:
  - well documented exposures
  - several confounders controlled
  - well-conducted statistical analysis.
- Statistically significant effects seen on aneuploidy and structural aberration in sperm in low- and high-exposed groups (GM 1 and 7.7 ppm, respectively). Dose-response trend present.
- However, effects are within the normal control range seen in healthy men as reported in various studies
  - Baumgartner et al., 1999, McInnes et al., 1998, Van Hummeln et al., 1996, Sloter et al., 2000, Sloter et al., 2007

EXAMPLE 1 - HIGH SCORING STUDY, CERTAIN LOAEL – CLINICAL RELEVANCE (2)

- Xing, Ji, Marchetti studies:
  - Germ cell aneuploidy is expected to lead to infertility and pregnancy loss, but such effects are not a known phenomenon for benzene (DECOS, IARC)
  - Moreover, Marchetti et al report no difference between exposed and non-exposed groups in the values of 4 WHO sperm quality criteria (sperm concentration, sperm count, semen volume and % sperm motility)
  - Arguably the effects seen are within normal control range and not clinically relevant
  - However, since three studies reported the effect, we did not consider this an isolated finding, and the arithmetic mean (calculated from the geometric mean and GSD) of the low-exposed group > 1.6 ppm was considered the LOAEL.

EXAMPLE 2 – A HIGH SCORING STUDY, UNCERTAIN LOAEL (1)

- Swaen et al (2010) (score 18.5) studied several haematologic parameters
  - Detailed job-exposure matrix
  - Controls from same factory but unexposed to benzene
  - Confounders (age, smoking, time) controlled
  - 1760 workers, >20,000 blood tests (high power)
  - Most parameters not related to benzene except eosinophils:

EXAMPLE 2: A HIGH SCORING STUDY, UNCERTAIN LOAEL (2)

Table reproduced from Swaen *et al* 2010

LOAEL judged less certain – isolated finding

Haematological parameters in exposed and non-exposed workers after adjustment for smoking age and month at blood sampling. (Table 4)

Haematological parameter	Non-exposed [a] (12,173 samples)	Exposed [a] (8532 samples)	Benzene exposure [a] Categorical	Benzene exposure [b] Continuous	Smoking [b]	Age [b]
Haemoglobin (mmol/L)	9.4	9.392	0.02571*	0.0036	0.100***	−0.008***
Hematocrit (L/L)	0.5	0.456	0.0001	0.0022	0.003**	−0.0005***
White blood cells (_L)	6651.1	6706.9	55.8	39.1	1058.9***	−5.40*
Lymphocytes (_L)	2090.3	2097.02	6.73	17.02	167.43***	−1.23**
Neutrophils (_L)	3865.4	3881	15.65	12.9	848.7***	−10.23***
Eosinophils (_L)	182.6	181.58	−1.02	−20.55***	15.28***	1.59***
Basophils (_L)	42.1	46.33***	4.25***	2.36	2.38**	0.21***
Monocytes (_L)	478.6	503.13***	24.53***	5.15	44.31***	8.19***

[a] In regression model with categorical exposure (0 = no, 1 = yes), smoking (0 = no, 1 = yes), age (per 1 year increment) and month at blood sampling

[b] In regression model with continuous exposure (per 1ppm increment), smoking (0 = no, 1 = yes), age (per 1 year increment) and month at blood sampling

* $p < 0.05$ ** $p < 0.005$ *** $p < 0.000$

EXAMPLE 3 – NOAEL STUDY

- Pandey et al 2008 studied Indian petrol pump workers examining micronuclei (in 39 workers) and comet (in 100 workers) of peripheral lymphocytes. Controls were matched local workers with no fuel exposure
- Quality score was 15.5 - top tertile
- Blood benzene levels determined - suggested significant dermal uptake
- Low benzene exposure (blood benzene~4ppb) had no excess of MN cf control (NOAEL)
- High benzene exposure (blood benzene~15ppb) had excess of MN cf control (LOAEL)
- DFG correlation (benzene : blood/air) indicates NOAEL is ~ 0.9ppm (and LOAEL is ~ 2ppm)

EXAMPLE 4 – LOW SCORING STUDY

- Testa et al 2005 studied structural chromosome aberrations and micronuclei (and SCEs) on 25 car spray workers from 8 workplaces compared to age/gender matched blood donors
  - Quality score : Total = 6/24: 3/7 for Exposure, 3/17 for other factors:

- **Exposures (tasks) were heterogenous**
- **Time of sampling not specified**
- **Area (not personal) exposure measurement used**
- **Specific analysis for benzene and other solvents**

- Complexity of paint exposures noted – significant co-exposures
- Minimal non-parametric significance testing used only
- Significant increase in cytogenetic damage. Authors indicate "It is difficult to relate this observed risk to each paint component"
- Concern for confounding by smoking – also cytogenetic damage greater in non-smokers than smokers
- Confounding by smoking and unclear if effects were due to benzene or other co-exposure meant low quality score

LOAELS AND NOAELS- METHODOLOGY

- LOAEL: lowest dose group (or point on a continuous curve) showing statistically significant effect versus control (or, rarely, lowest exposed group)
- NOAEL: highest exposure group showing no statistically significant effect versus control. Borderline significant findings not used for NOAEL
- Representative exposure within LOAEL/NOAEL group sought. Preference for representative exposure:
  - Arithmetic mean
  - Median or geometric mean
  - Category midpoint
  - Percentile points other than 0.01 or 0.99
- Biologic effect of LOAELs difficult to assess due to lack of historic controls.
- LOAELS and NOAELS were not always present due to
  - equivocal findings
  - no representative exposure possible
  - insufficient quantitative information

LOAELS AND NOAELS- CERTAINTY RATINGS

Certainty ratings for LOAELs and NOAELs.

Uncertain if:

- LOAEL based on <10 or NOAEL based on <20
- Non-monotonic dose response
- Effect only in subgroup
- Effect an isolated finding
- Likely confounding from a co-exposure
- Unresolvable biomarker/air exposure disagreement

SUMMARY OF LOAELS AND NOAELS IRRESPECTIVE OF HIGH OR LOW CERTAINTY, AND EXPOSURE CONTEXT

Haematotoxicity

- 30 studies scored after combining like populations
  - 16 at or above median score of 12.5 (out of 24)
  - 10 allow for a LOAEL (0.04 – 8 ppm, median 2.6 ppm)
  - 10 allow for a NOAEL (0.19 – 3.5ppm, median 0.68 ppm)
  - 5 allow for both a LOAEL and NOAEL

Genotoxicity

- 59 studies scored after combining like populations
  - 31 at or above median score of 11.5 (out of 24)
  - 17 allow for a LOAEL for CA, MN, Aneusomy (0.006 – 13.6 ppm, median 1.6-1.9 ppm)
  - 11 allow for a NOAEL for CA, MN, Aneusomy (0.001 – 8 ppm, median 0.3 ppm)
  - 5 allow for both a LOAEL and NOAEL for CA, MN, Aneusomy

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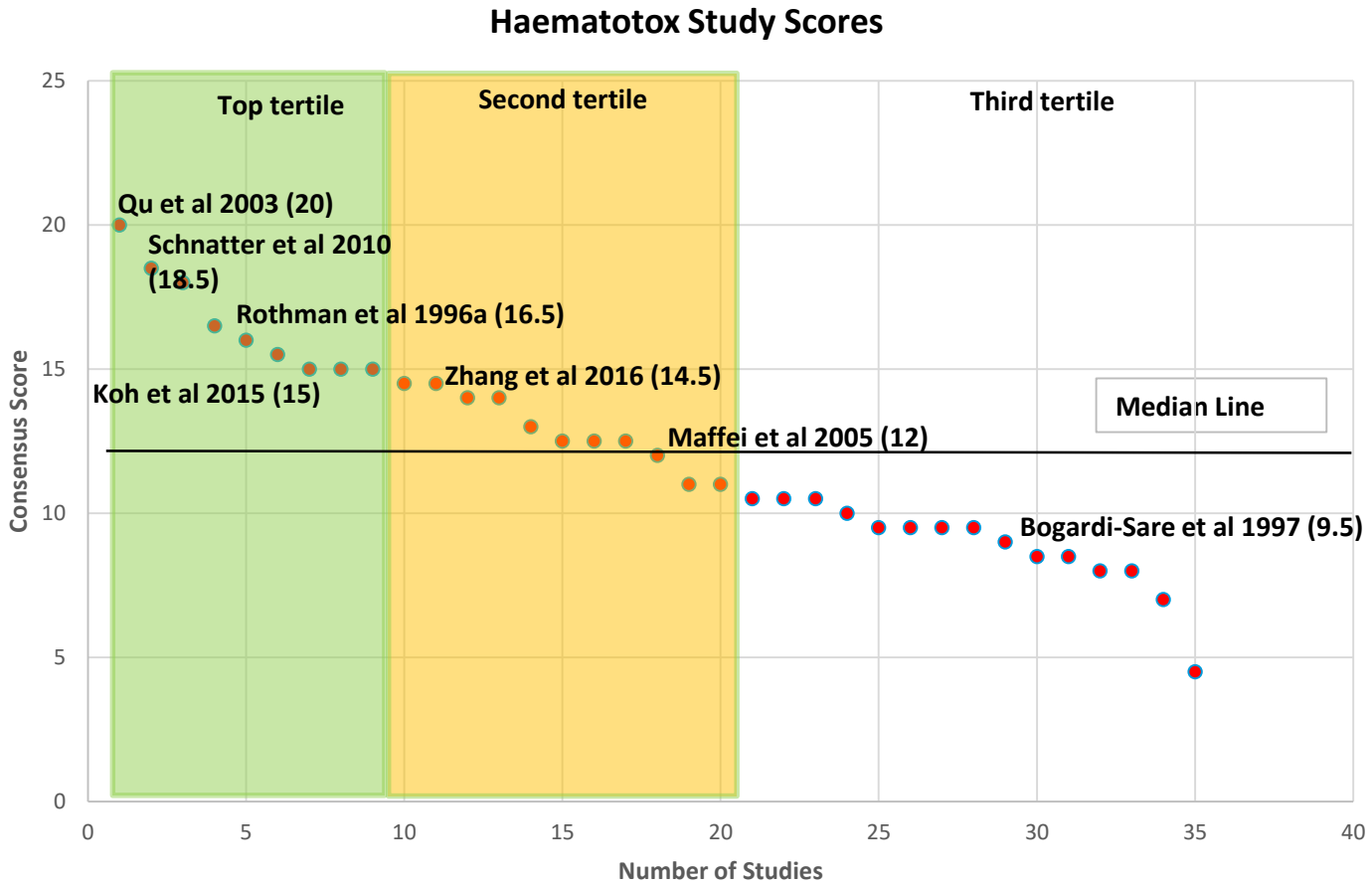
HAEMATOTOXICITY STUDY SCORE DISTRIBUTION



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HAEMATOTOXICITY STUDIES ABOVE MEDIAN QUALITY SCORE

Author	Score	Endpoint	LOAEL	NOAEL
Qu et al 2003	20	Neutrophils	2.26	None
Swaen et al 2011	18.5	Eosinophils	0.75	0.25
Schnatter 2010	18	Neutrophils	7.8	2.9
Ward et al 1996	17	Leukopenia	7.2	2.2
Collins et al 1991	16.5	Several	None	0.19
Rothman et al 1996	16.5	Lymphocytes	7.6	None
Lan et al 2004	15.5	B-cells	2.2	None
Koh et al 2015	15	Anemia	2.6	0.21
Pesatori et al 2009	15	CBC	None	1.7
Casale et al 2016	14.5	Neu, Lym	NA	NA
Zhang et al 2016	14.5	WBC	>2.1	None
Collins et al 1997	14	Lymphopenia	None	0.55
Tsai et al 2004	13	CBC	None	0.33
Bogadi-Sare et al 2003	12.5	CBC	8	3.5
Khuder et al 1999	12.5	CBC	None	0.81
Li et al 2018	12.5	CBC	0.04	None

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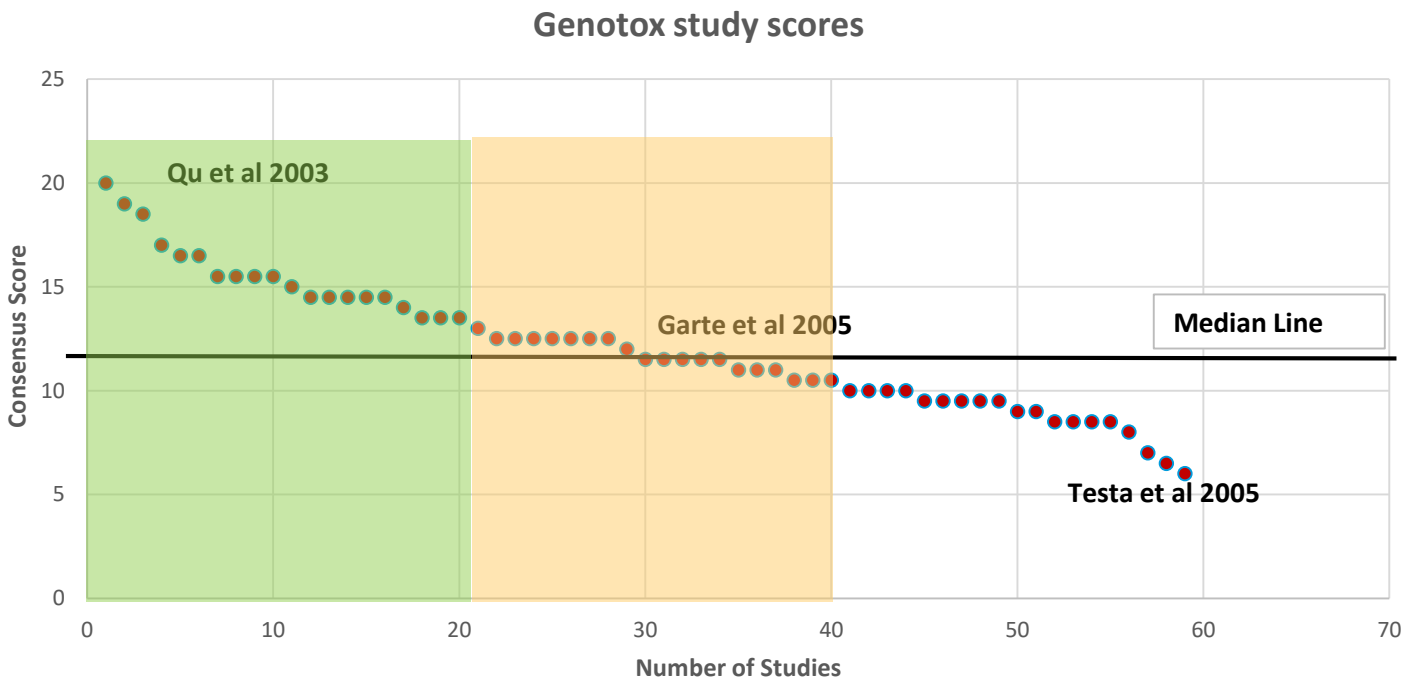
GENOTOXICITY SCORE DISTRIBUTION



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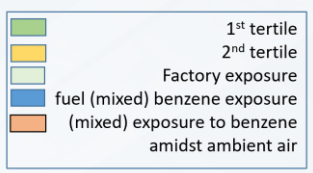
GENOTOXICITY STUDIES ABOVE MEDIAN QUALITY SCORE

Author	inal Scor	Endpoint	LOAEC (ppm)	Note	NOAEC (ppm)	Note
Qu et al 2003	20	CA	3.07			
Xing et al 2010(19), Ji et al 2012 (18), Marchetti et al 2012	19	sp aneuploidy	>1.6			
Krieg et al 2012*	18.5	Comet			0.274	
Kim 2004 (coke)*	16.5	t(8,21), aneuploidy, (8,21)	>0.557			
Arayasiri et al 2010*	16.5	Comet			0.012	
Zhang 2012 set (Lan et al 2004 associated genetox studies)	15.5	Aneuploidy	>2.64		≤2.64	
Ruchirawat , M., et al. (2010)*	15.5	DNA repair capacity	0.025	(n = 31)		
Violante et al 2003*	15.5	MN			0.0051	
Carere et al 1995	15	CA, MN	2		0.46	
Zhang et al 1998 set (Rothman 1996a associated studies)	14.5	CA (& breaks)	13.6	median	NA	
Zhang et al., 2014 (14.5) and Zhang et al 2016 (16)	14.5	MN	2	Zhang et al 2014		
Rekhadevi et al 2010, 2011	14.5	MN	1	MN		
Basso et al 2011*	14.5	MN			0.029	MN
Leopardi et al 2003	14.5	MN			0.0029	
Pandey et al 2008	14	MN	2	1-1.5 Comet	0.9	MN
Navasumrit et al 2005*	13.5	Comet	0.073			
Maffei et al 2005	13.5	MN	0.0076	4 hour	0.00135	4 hour
Carere et al 2002 *	13.5	Comet			3 ppb	
Bogardi-Sare et al 1997 (12.5); Bogardi-Sare 2003 (12.5)	12.5	CA	13		8	
Eastmond et al 2001 (Estonia)	12.5	CA (transloc)	1.3			
Holz et al 1995	12.5	MN	1	MN		
Fracasso et al 2010	12.5	CA			0.012	CA
Pitarque et al 1996	12.5	MN			0.3	
Goethel et al 2014	12.5	MN(Buc E)			0.6	Buccal MN
Angelini et al 2011, 2012*	12.5	MN	0.006	MN		
Kim et al 2010, Kim et al 2004a refinery, Kim et al 2008	12	CA, aneuploidy C7,C9	0.51			
Garte et al 2005*	11.5	DNA SSB	0.34			
Sul et al 2005*	11.5	Comet	~1.55			
Sarto et al 1984*	11.5	CA	>= 1.9			
Bukvic et al 1998	11.5	MN	0.071	MN		
Nilsson et al 1996*	11.5	DNA SSB			0.13	

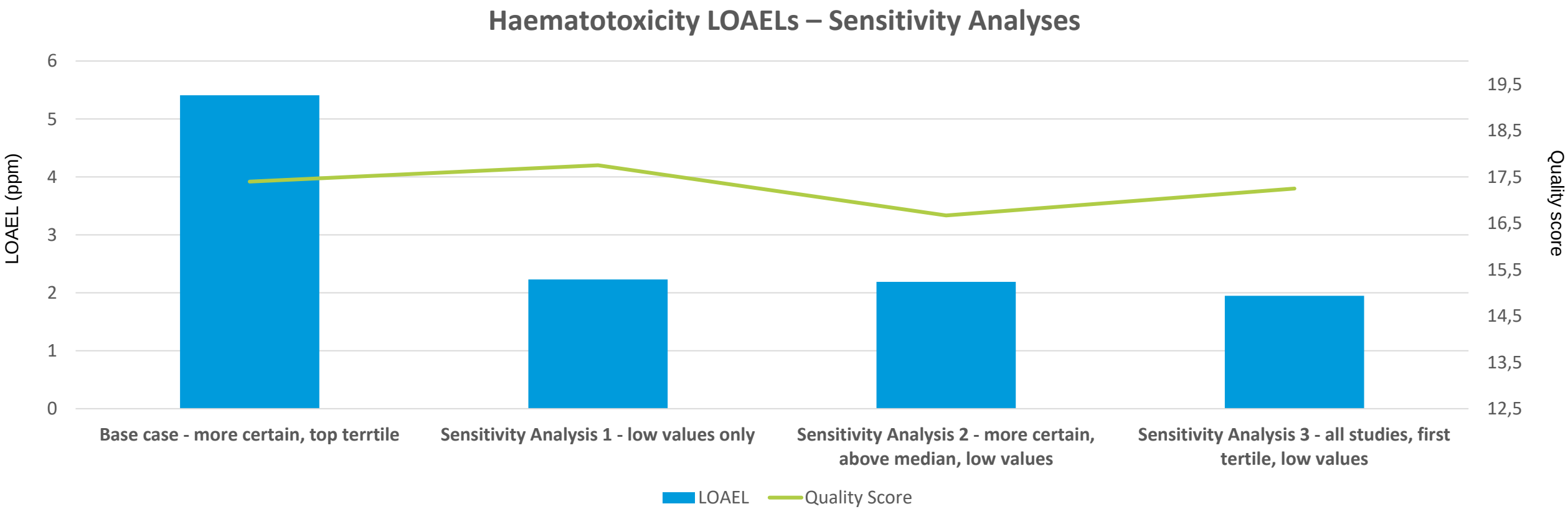


LOAELS AND NOAELS FOR HAEMATOTOXICITY

- Two clusters of LOAELs: **2- 3.5 ppm** (**3 studies**) **and 7-8 ppm** (**4 studies**)
- Three clusters of NOAELs: **2-3.5 ppm** (**4 studies**), **0.6 – 0.8 ppm (2 studies), 0.2 – 0.3 ppm (4 studies)**
- If highest NOAEL is given preference: ~3ppm NOAEL and 7 ppm LOAEL
- If lowest LOAEL is given preference: ~2ppm LOAEL and ~ 0.5 ppm NOAEL
- Latter scenario (2 ppm LOAEL and 0.5 ppm NOAEL) advanced as base case
  - Note that this aligns with genotoxicity

	More definitive studies (above median)	
Benzene concentration	Number of studies (LOAEL)	Number of studies (NOAEL)
~ 0.2 – 0.3 ppm	0	4
~ 0.6 – 0.8 ppm	0	2
~ 2 – 3.5 ppm	3	4
~ 7 – 8 ppm	4	0

HAEMATOTOXICITY LOWEST OBSERVED ADVERSE EFFECT LEVELS



LOAELS AND NOAELS FOR GENOTOXICITY

LOAEL based on top tertile, factory, most certain studies:

- Qu et al., 3.07 ppm
- Xing et al., >1.6 ppm
- Zhang et al 2012, >2.64 ppm
- Smith et al, 13.6 ppm (excluded)
- Zhang et al 2014, 2 ppm

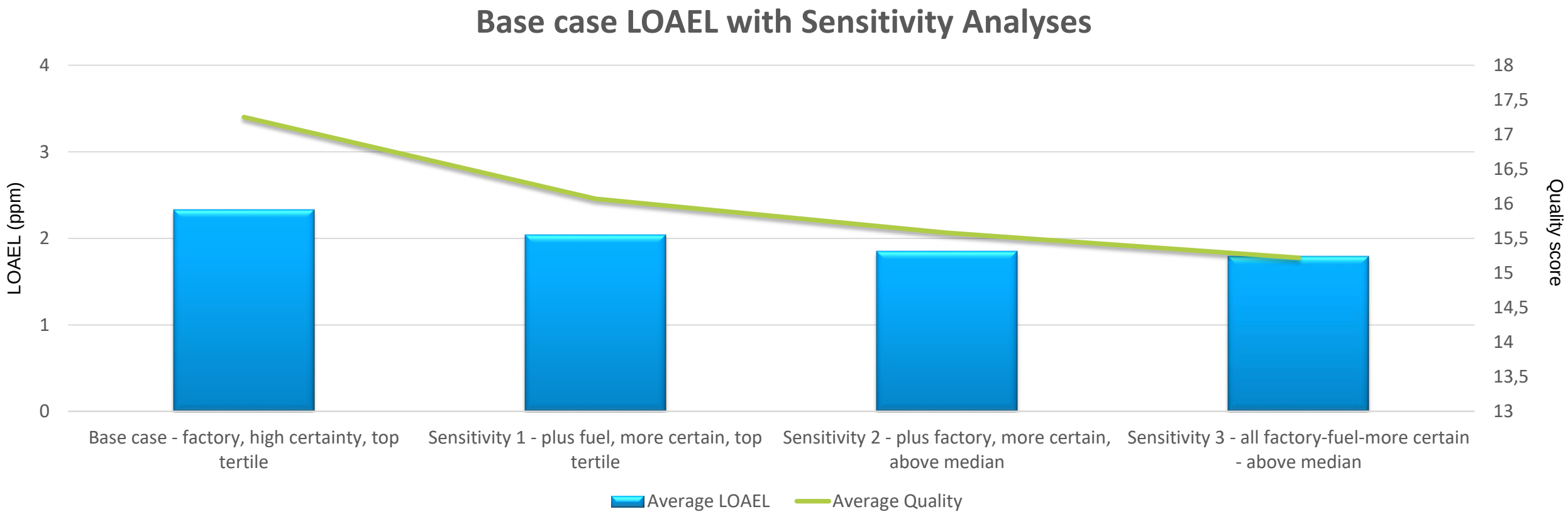
LOAEL: 2.3 ppm

NOAEL based on top tertile, fuel, most certain studies:

- Carere 0.46 ppm
- Pandey 0.9 ppm
  - Note -Factory studies too divergent (8 ppm and 0.07 ppm)

NOAEL: 0.68 ppm

GENOTOXICITY LOWEST OBSERVED ADVERSE EFFECT LEVELS



OEL BASED ON BEST QUALITY STUDIES (GENOTOXICITY AND HAEMATOTOXICITY)

Based on top tertile studies and top half studies

- WoE Haematotoxicity and Genotoxicity LOAELs: 2ppm
- WoE Haematotoxicity and Genotoxicity NOAELs: 0.5ppm
- Data support an OEL of 0.5ppm /8h via either the LOAELs and/or the NOAELs

OEL:

- (a) LOAEL (2 ppm): Overall assessment factor (LOAEL to NOAEL) = 4
  - 2/4 → **OEL = 0.5 ppm/8h**
- (b) NOAEL (0.5 ppm): No factors needed – large, diverse populations
  - → **OEL = 0.5 ppm /8h**
- Additional factor of 2 may be justified for genotoxicity blood/bone marrow sensitivity
  - → **OEL = 0.25 ppm/8h**

DISCUSSION

Strengths

- OELs based on weight of evidence, highest quality information
- Objective criteria used to rank best studies and base conclusions on the most informative studies
- Thorough sensitivity analyses used to assess impact of assumptions made about quality
- Based on Human data – so no interspecies uncertainty

Weaknesses

- Even the very best studies still have shortcomings – clinical relevance, role of confounders still open questions
- Literature shows some basic flaws in most studies – co-exposures, confounder assessment methodology, role of genetic susceptibility
- Focused only on genotox., haematotox. – not other endpoints i.e. immunotoxicity

CONCLUSIONS

- Rich, diverse literature on benzene can be assessed using quality scoring methods, allowing conclusions to be based on methodologically-sound studies
- Every study has shortcomings; many have multiple shortcomings
- Best quality information supports effects at 2 ppm or higher
- Best quality information suggests no effects at 0.5 ppm and lower
- Extra adjustment factor allows for possible sub-clinical effects in bone marrow
- 0.25 ppm is a well supported OEL for benzene exposure

LOA BENZENE WORK GROUP - CONTRIBUTORS TO THIS WORK

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Thank you for your attention!

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BACKUP

LIMITATIONS OF THE HIGHEST SCORING STUDY FROM INSUFFICIENT ATTENTION TO CONFOUNDERS

Table 7. Differences in Blood Cell Counts Between Unexposed Subjects and Subjects with 4-Week Mean Benzene Exposures of 0.5 ppm or Lower[a]

Variable	Unexposed	Exposed (>0 to 0.5 ppm)	Significant *P* value[b]
Number of subjects	51	16	NA
Female (%)	53	100	NA
Smoker (%)[c]	31	0	NA
Age (years)	33.3±7.4	36.2±3.2	NA
4-Week mean benzene exposure	0.004±0.003	0.14±0.04	—
Red blood cells ($\times 10^{10}$/L)	463±52	393±49	0.0006
Hematocrit	44.2±5.3	43.1±2.6	—
Platelets ($\times 10^{9}$/L)	277±43	286±71	—
White blood cells ($\times 10^{6}$/L)	6671±1502	5700±1226	0.02
Lymphocytes ($\times 10^{6}$/L)	2205±789	2015±450	—
Neutrophils ($\times 10^{6}$/L)	4006±1108	3254±901	0.02
Monocytes ($\times 10^{6}$/L)	267±139	251±108	—
Eosinophils ($\times 10^{6}$/L)	145±162	136±133	—
Basophils ($\times 10^{6}$/L)	9.3±19.3	10.1±14.6	—
Band cells	32.6±44.1	33.5±40.3	—
Atypical lymphocytes	0.10±0.22	0.04±0.11	—

[a] Values are given as means ± SD of the raw variables; but for the monocytes, eosinophils, and basophils, the statistical tests were performed on the log-transformed data.

[b] Least-squares regression analysis controlling for sex, age, smoking, cotinine level, toluene exposure, and year (phase) of study. NA = not applicable. Dashes indicate $P \geq 0.05$.

[c] Includes self-reported smokers and subjects with cotinine levels >100 μg/g creatinine.

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BACKUP

HAEMATOTOXICITY: LOWEST OBSERVED ADVERSE EFFECT LEVELS

AUTHOR	LOAEL	Score	Avg. LOAEL	Avg. Score	Notes
FIRST TERTILE - MORE CERTAIN					
Qu	2.26	20.00	2.26	20.00	Best study
Schnatter	7.80	18.00	5.03	19.00	
Ward	7.20	17.00	5.75	18.33	
Rothman	7.60	16.50	6.22	17.88	
Lan	2.20	15.50	5.41	17.40	
All 1st T, more cert.			6.22	17.88	Leading case
All 1st T, more certain, lower values			2.23	17.75	Sensitivity analysis #1
SECOND TERTILE, ABOVE MEDIAN - MORE CERTAIN					
Zhang, 2016	2.10	14.50	2.10	14.50	
Bogadi-Sare, 2003	8.00	12.50	5.05	13.50	
All above median, more cert.			5.31	16.29	Sensitivity analysis #2
All above med, more cert. lower values			2.19	16.67	Sensitivity analysis #3
SECOND TERTILE, BELOW MEDIAN - LESS CERTAIN					
No such studies					
FIRST TERTILE - LESS CERTAIN					
Swaen	0.75	18.50			
Koh	2.60	15.00	1.68	16.75	
All 1st tertile only			4.34	17.38	Sensitivity analysis #4
All 1st tertile, lower values			1.95	17.25	Sensitivity analysis #5

Lower Olefins and Aromatics Reach Consortium (LOA)

BACKUP

GENOTOXICITY: LOWEST OBSERVED ADVERSE EFFECT LEVELS

AUTHOR	LOAEL	Score	Avg. LOAEL	Avg. Score	Notes
FIRST TERTILE - MORE CERTAIN					
Qu et al 2003	3.07	20.00			Best study
Xing et al 2010	1.60	19.00	2.34	19.00	
Zhang et al 2012	2.64	15.50	2.44	17.25	
Smith et al 1998	13.60	14.50			Excluded - high exposure
Zhang et al 2014	2.00	14.50	2.33	17.25	
All 1st T, more cert, factory			2.33	17.25	Leading case
FIRST TERTILE - MORE CERTAIN					
Carere et al 1995	2.00	15.00	2.00	15.00	
Rekhadevi	1.00	14.50	1.00	14.75	
Pandey	2.00	14.00	1.75	14.63	
Factory and Fuel 1st T, more certain			2.04	16.07	Sensitivity analysis #1
SECOND TERTILE, ABOVE MEDIAN - MORE CERTAIN					
Bogadi-Sare	13.00	12.50			Excluded - high exposure
Eastmond	1.30	12.50	1.30	12.50	
Kim, 2010	0.51	12.00	0.91	12.25	
All above median, factory			1.85	15.58	Sensitivity analysis #2
SECOND TERTILE, ABOVE MEDIAN - MORE CERTAIN					
No such studies					
All above median, factory and fuel			1.79	15.22	Sensitivity analysis #3
FIRST TERTILE – LESS CERTAIN					
Kim (Coke)	0.56	16.50	0.56	16.50	
All 1st T only, factory			1.97	17.10	Sensitivity analysis #4
All of the above			1.67	15.71	Sensitivity analysis #5