



Martijn Rooseboom¹, Neslihan Aygun Kocabas², Richard James Radcliffe³, Lawrence Segal⁴

¹Shell, The Hague Netherlands; ²TotalEnergies, Senefelt Belgium; ³Penman Consulting Ltd, Wantage UK; ⁴Penman Consulting BVBA, Brussels Belgium

Conflict of Interest: The authors declare that there is no real or perceived conflict of interest. The authors are employed by entities that manufacture or distribute the material that is subject to this presentation or have received services fees from those entities.

The Lower Olefins and Aromatics REACH Consortium undertook an independent evaluation of the **Occupational Exposure Limit (OEL)** for Toluene.

Methods

PBPK Modelling

Relevant human (occupational) and mammalian literature were obtained from:

- Previous regulatory reviews and their references (105 in total).
- Literature Search (31/12/16 – 07/02/22). 84 initial hits were screened, 24 results were retained.

Literature relevant to the critical effects (**CNS/Neuro-behavioural toxicity**, **Ototoxicity**, **Colour Vision**, and **Reproductive and Developmental toxicity**) were reviewed for:

- Relevance
- Quality
- Klimisch Criteria (animal data only)

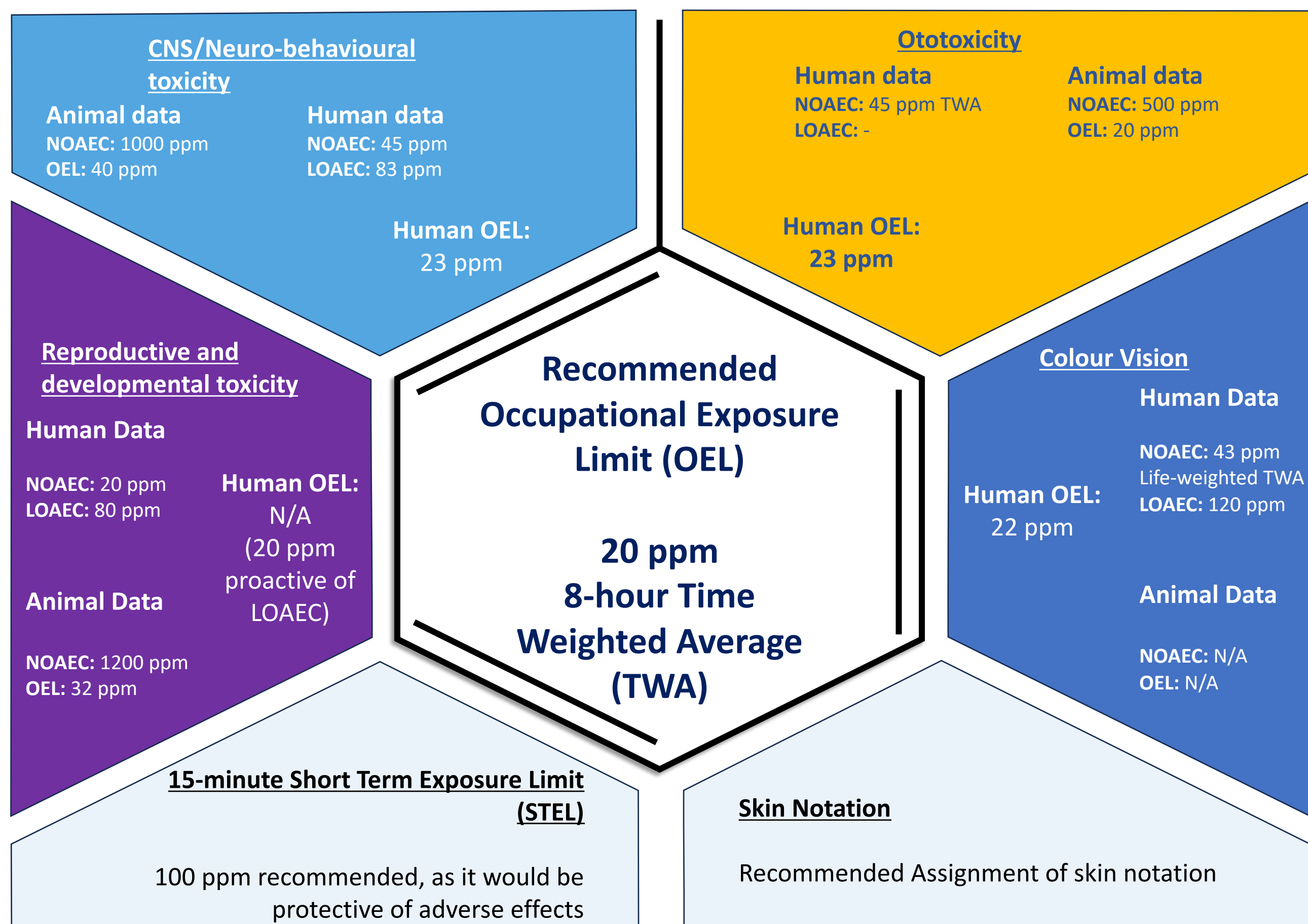
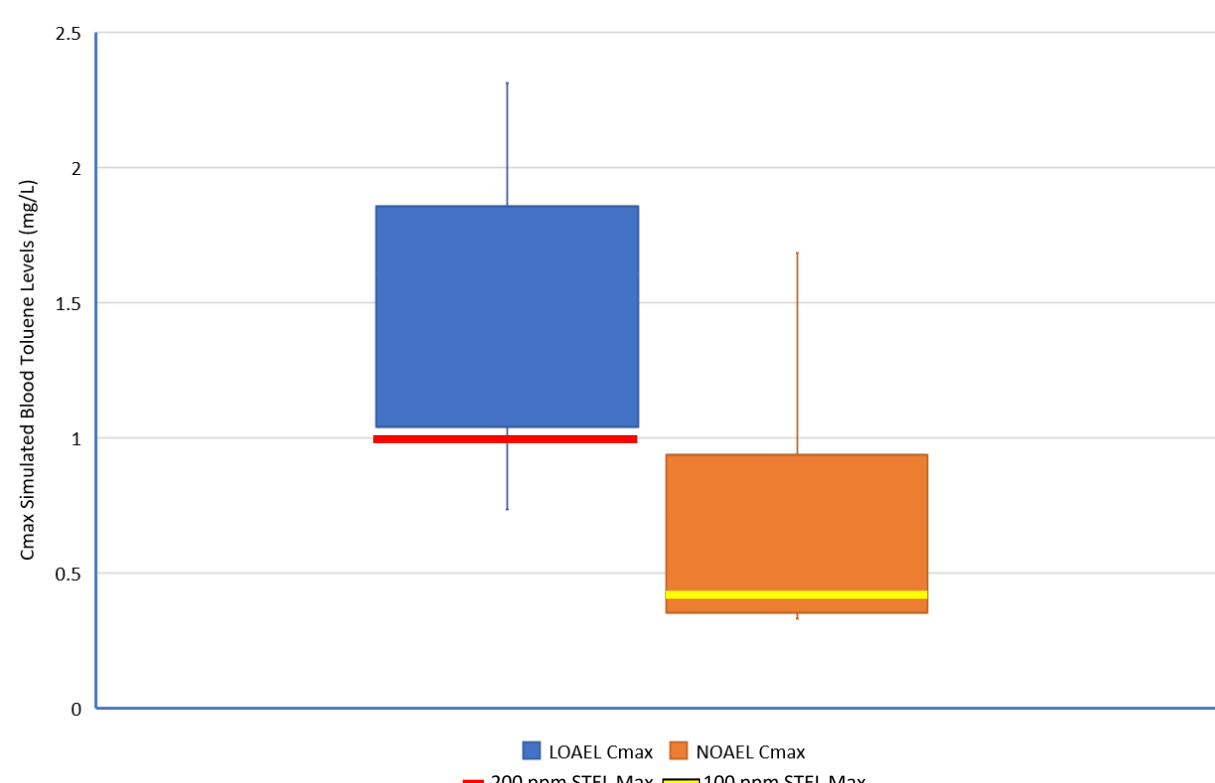
OELs for the critical effects were calculated from human and animal data using standard ECHA guidance with justified assessment factors.

Dermal absorption was calculated using literature values to determine if a skin notation was required.

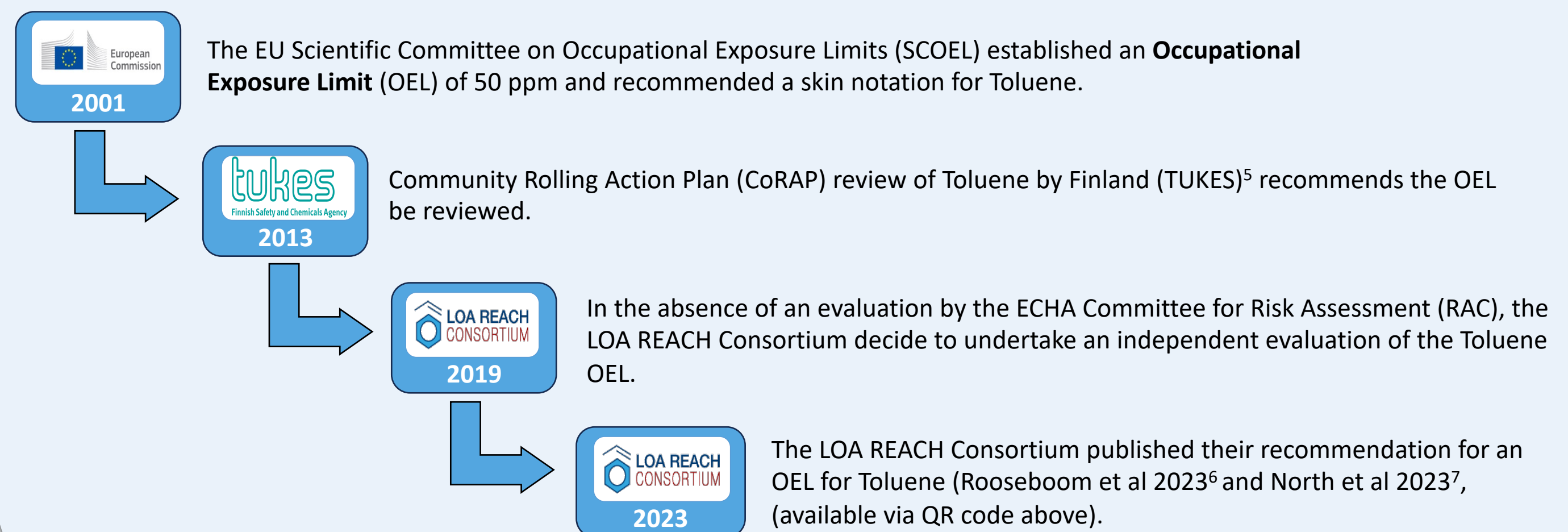
The blood concentrations of studies that provided NOAEC or LOAEC values were simulated via an existing physiologically-based pharmacokinetic (PBPK) model.

Short Term Exposure Limit (STEL)-like exposure scenarios were simulated at the following peak exposures:

- 100 ppm – maximum toluene blood concentration was 0.4 mg/L (lower quartile of simulated NOAEC studies)
- 200 ppm – maximum toluene blood concentration was 1 mg/L (lower quartile of simulated LOAEC studies)



Background



Methods

- Majority of publications assessing toluene were from previous regulatory reviews and documentation^{5, 8-11}, or included in the current LOA Toluene REACH dossier (105 in total). An additional literature search for publications between 31 December 2016 – 7 February 2022 was performed. 84 hits were screened for applicability to Toluene and REACH, and 24 references were retained.
- LOA evaluated the following critical effects of toluene exposure:
 - Central nervous system and neuro-behavioural toxicity**
 - Ototoxicity**
 - Colour vision effects**
 - Reproductive and developmental toxicity**
All human-related publications were assessed for **relevance** and **quality**. All animal-related publications were assessed via the **Klimisch criteria**¹² (only scores of 1 or 2 were retained)

- OELs were then derived using the most conservative NOAEC values using the standard ECHA guidance¹³, with the following **assessment factors**:
 - Human intraspecies uncertainty AF – 2**
The default value in the ECHA 2012 guidance is 5. However, the human occupational studies used resulted in a large, diverse, and sufficiently detailed worker population (see Table 1); therefore most, if not all, factors causing human variability are covered.
 - Animal developmental toxicity study on exposure duration AF – 1**
Based on CEFIC guidance¹⁴, as the exposure duration in the analysed studies covered the entire development of the offspring.

Critical Effect	Total participants	Exposed participants/cases	Control/Referents
CNS/neuro-behavioural toxicity	1440	847	593
Ototoxicity	978	575	403
Colour vision effects	980	667	332
Reproductive and developmental toxicity	2381	1410	971

Table 1: Number of human subjects in assessed human occupational studies. Total participants screened for repeat populations.

- The WG also assessed if a **skin notation** based on ECETOC criteria and a **15-minute Short Term Exposure Limit (STEL)** based on PBPK modelling (Berkley Madonna 9.0, Berkeley Madonna, Inc., Albany, CA) were needed at the derived OEL. Full details are available in North et al⁷.

Human NOAECs and LOAECs

The following **NOAECs** and **LOAECs** were identified from the highest quality studies of each critical effect:

CNS/Neuro-behavioural toxicity NOAEC: 45 ppm ^{15, 16} LOAEC: 83 ppm ¹⁷	Ototoxicity NOAEC: 45 ppm TWA ^{18, 19} LOAEC: no high-quality studies identified	Reproductive and developmental toxicity NOAEC: 20 ppm ²⁰ LOAEC: 88 ppm ²⁰	Colour Vision NOAEC: 43 ppm life-weighted TWA ²¹ LOAEC: 120 ppm ²²
---	--	--	---

Calculated Human OELs

CNS/Neuro-behavioural toxicity OEL: 23 ppm	Ototoxicity OEL: 23 ppm	Reproductive and developmental toxicity OEL: None (20 ppm protective)	Colour Vision OEL: 22 ppm
--	-----------------------------------	---	-------------------------------------

The OELs derived for CNS/Neuro-behavioural toxicity, Ototoxicity, and Colour Vision can be rounded to **20 ppm** for an 8-hour TWA. **Reproductive and developmental toxicity studies** were not deemed high enough quality for a Point of Departure to derive an OEL. However, one study²⁰ was considered to provide a safety signal that was used as the basis of a risk assessment in humans (reported NOAEC 25 ppm, LOAEC 88 ppm). Therefore, an OEL of 20 ppm is considered protective for all endpoints evaluated.

Acknowledgements: The authors would like to thank Colin North (Formerly ExxonMobil, currently BASF) for his graphical input and Larry Higgins (Penman Consulting Ltd) for helpful discussion and input.

References

- TUKES (2013) Substance Evaluation Report. Background document for the purpose of substance evaluation under REACH for Toluene (EC No 203-625-9, CAS No 108-88-3) Finnish Safety and Chemicals Agency (Tukes) 12 November 2013
- Rooseboom, M., Kocabas, N.A., North, C., Radcliffe, R.J. and Segal, L., 2023. Recommendation for an occupational exposure limit for toluene. Regulatory Toxicology and Pharmacology, 105387 – download for free with the QR code!
- North, C.M., Rooseboom, M., Kocabas, N.A., Synhaeve, N., Radcliffe, R.J. and Segal, L., 2023. Application of physiologically-based pharmacokinetics modelled toluene blood concentration in the assessment of short term exposure limits. Regulatory Toxicology and Pharmacology, 140, p.105380. – download for free with the QR code!
- ATSDR (2017) Toxicological Profile for Toluene. Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, US Dept for Health and Human Services. June 2017
- ACGIH (2007) Toluene. TVI documentation. American Conference of Governmental Industrial Hygienists.
- ACGIH (2020) Toluene. TVI documentation. American Conference of Governmental Industrial Hygienists
- SCOEL (2001) EU Scientific Committee on Occupational Exposure Limits (SCOEL). Recommendation from the Scientific Committee on Occupational Exposure Limits for toluene. SCOEL/5/04/18
- Klimisch, H.J., Andreae, M. and Tillmann, U., 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regulatory Toxicology and Pharmacology, 15(1), pp.1-5.
- ECHA (2012) Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose (concentration)-response for human health. Version: 2.1 November 2012. https://echa.europa.eu/documents/10162/13632/information_requirements_en.pdf?457242ba-0700-4d4c-8006-88466223268
- CEFIC (2014) FCA Guidelines on Risk Assessment of non-listed substances (NLS) and non-intentionally added substances (NIAS) under the requirements of Article 3 of the Framework Regulation (EC) 1935/2004 Version 1.0 October 2016
- Seeber, A., Schaper, M., Zupanic, M., et al. (2004) Toluene exposure below 50 ppm and cognitive function: A follow-up study with four repeated measurements in rotogravure printing plants. Int Arch Occup Environ Health 22(1):1-9
- Zupanic, M., Seeber, A. (2002) Psychomotor performance and subjective symptoms at low level toluene exposure. Occup Environ Med 59:263-268
- Matsushita, Y., Arimatsu, Y., Ueda, A., et al. (1975) Hematological and neuromuscular response of workers exposed to low concentration of toluene vapor. Ind Health 13:115-121
- Schaper, M., Dumes, P., Zupanic, M., et al. (2003) Occupational toluene exposure and auditory function: Results from a follow-up study. Ann Occup Hyg 22(6):493-502
- Schaper, M., Seiber, A., van Thriel, C. (2008) The effects of toluene plus noise on hearing threshold: An evaluation based on repeated measurements in the German printing industry. Int J Occup Med Environ Health 21(3):193-200
- Ng, T.P., Foo, S.C., Young, T. (1992) Risk of spontaneous abortion in workers exposed to toluene. British Journal of Industrial Medicine 49:804-808
- Berkley Madonna 9.0, Berkeley Madonna, Inc., Albany, CA
- Seiber, M., Dumes, P., Klesswetter, E., et al. (2004) Colour vision and occupational toluene exposure: Results of repeated examinations. Toxicol Lett 153(1):193-202
- Zavile, M., Mandic, Z., Turk, R., et al. (1998) Assessment of colour vision impairment in male workers exposed to toluene generally above occupational exposure limits. Occup Med 48(3):175-180
- Beasley, T.E., Eversley, P.A., Bushnell, P., et al. (2010) Behavioral effects of subchronic inhalation of toluene in adult rats. Neurotoxicol Teratol 32(6):611-619.
- Beasley, T.E., Eversley, P.A., Bushnell, P., et al. (2012) Behavioral effects of sub-acute inhalation of toluene in adult rats. Neurotoxicol Teratol 34(1):83-89
- Lund, S.P. and Kristiansen, G.B. (2008) Hazards to hearing from combined exposure to toluene and noise in rats. Int J Occup Med Environ Health 21(1):47-57
- Hass, U., Lund, S.P., Hougaard, K.S. and Simonsen, L. (1999) Developmental neurotoxicity after toluene inhalation exposure in rats. Neurotoxicol. Teratol. 21(4): 349-357
- Monster, A. et al. (1993) Evaluation of biological monitoring parameters for occupational exposure to toluene. Int Arch Occup Environ Health 65(Suppl):159-162 (<https://link.springer.com/article/10.1007/BF00381332>)
- ECETOC (2012). Technical Report No. 114 ECETOC TRA version 3: Background and rationale for its improvements

Evaluation of Animal Data

No animal studies were considered suitable as a Point of Departure for the colour vision endpoint. For the other critical effects, the OELs derived from Human occupational data were generally more conservative than those derived from animal studies (Table 2), therefore the recommended 20 ppm OEL was considered justified.

Critical Effect	Animal NOEC	Animal OEL	Human OEL
CNS/neuro-behavioural toxicity	1000 ppm ^{23, 24}	40 ppm	23 ppm
Ototoxicity	500 ppm ²⁵	20 ppm	23 ppm
Colour vision effects	No study identified as a point of departure	-	22 ppm
Reproductive and developmental toxicity	1200 ppm ²⁶	32 ppm	20 ppm considered protective

Table 2: Animal Occupational Exposure Limits derived from Animal NOAEC data, and OELs derived from Human data for comparative purposes

Skin Notation

Dermal absorption was calculated to determine if it could contribute systemic toluene toxicity. A **skin notation** should be applied if dermal absorption of toluene in 1 hour is greater than 10% of the toluene absorption via the lungs at the proposed 20 ppm 8-h TWA OEL for 8 hours (calculated to be 375 mg). Using literature flux data²⁷ for absorption via hands and forearms (~2000 cm² area) a dermal absorption was 1000 mg of toluene in 1 h, far exceeding recommended criteria²⁸. Therefore, a skin notation was **recommended**.

Short Term Exposure Limit (STEL)

The peak blood toluene concentrations of 14 CNS/Neuro-behaviour studies were simulated to determine if a STEL was required (Figure 1).

STEL-like scenarios were then modelled using the following assumptions:

- 60 kg body weight for test subjects
- Light work activity
- Cardiac output equal to alveolar ventilation rate
- Exposures limited to 15 mins each, with 1 hour between exposure, four exposures per shift.

The peak exposures chosen for the STEL-like scenarios were at 100 ppm and 200 ppm to reflect a 20 ppm and 40 ppm 8-h TWA OEL respectively. In both scenarios, blood toluene levels rose rapidly but did not complete clearance before the beginning of the next exposure (Figure 2).

- At 100 ppm, the highest blood toluene concentration was ~0.4 mg/L (Figure 2), a value similar to the lower quartile values of the simulated NOAECs (represented by diamond labelled 100 ppm STEL, Figure 1).
- At 200 ppm, the highest blood toluene concentration was 1 mg/L (Figure 2), within the range of the lower quartile values of the simulated LOAECs (represented by diamond labelled 200 ppm STEL, Figure 1).

Therefore, the data showed that a **100 ppm STEL** would be **protective** against adverse effects.

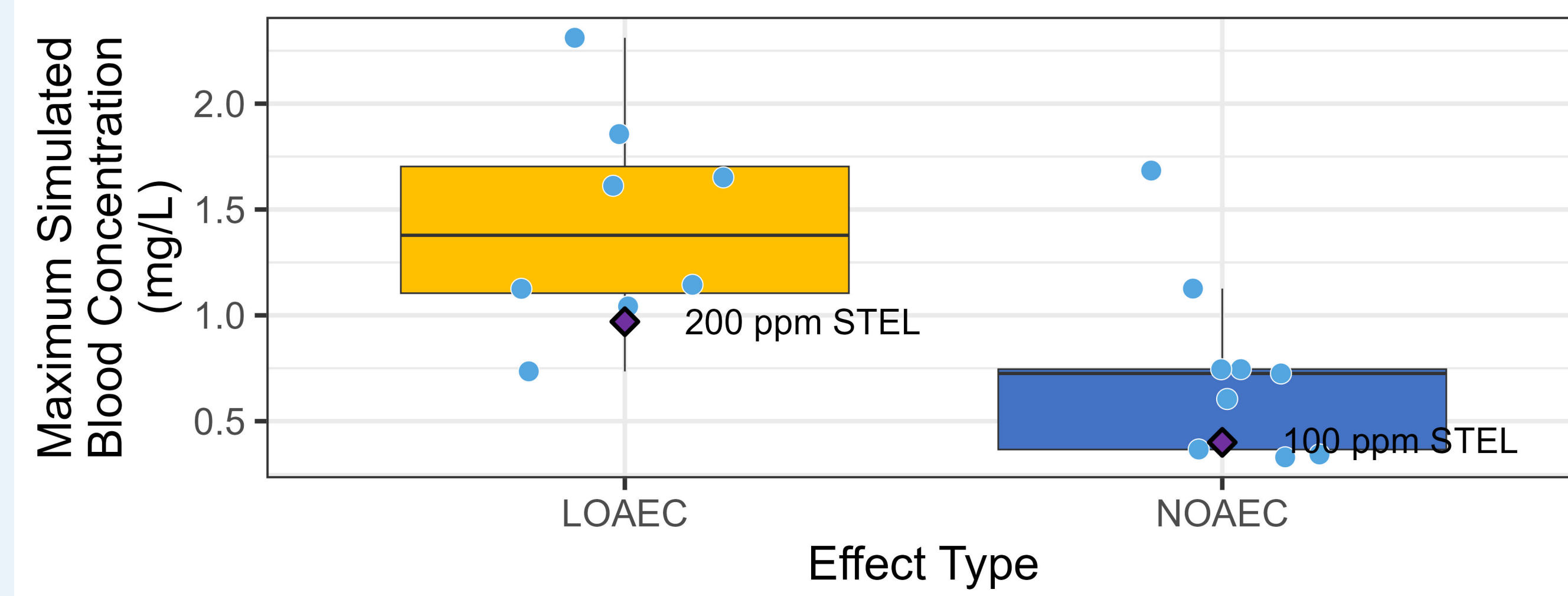


Figure 1: Range of Simulated Maximum Blood Concentration for LOAEC and NOAEC values. Purple diamonds denote peak blood toluene concentration of STEL-like exposure scenarios (see Figure 2).

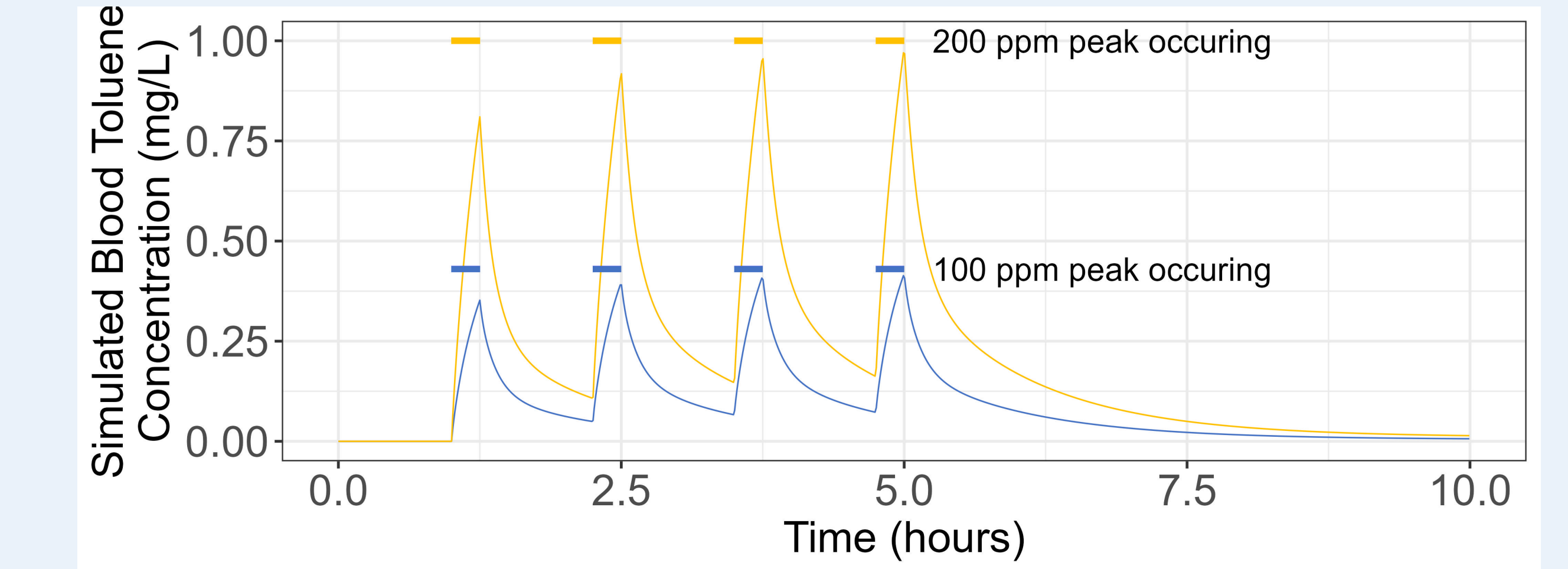


Figure 2: Time course of simulated blood toluene concentration in 100 ppm and 200 ppm STEL-like exposure scenario

Conclusions

After independently evaluating the available data of Critical Effects from the highest quality Human studies available, the WG found that the derived OELs of all Critical Effects were 20 ppm. Therefore, LOA recommends a **20 ppm 8-h TWA**.

The WG also found that a **Skin Notation should also be applied**, and as a result of the PBPK modelling, the short-term CNS and Neurobehavioral studies supported a **100 ppm 15-min STEL** at a 20 ppm OEL.