| Compound | 1,2,4,5-Tetramethylbenzene (read-across from trimethylbenzenes) | | Factsheet |
|---|---|---|---|
| **Parameter** | **Note** | **Comments** | **Value / descriptor** |
| **EU-LCI value and status** | | | |
| EU-LCI value | 1 | Mass/volume [µg/m$^3$] | 250 |
| EU-LCI status | 2 | Draft/final | Final |
| EU-LCI year of issue | 3 | Year when the EU-LCI value was issued | 2016 |
| **General information** | | | |
| CLP Index No | 4 | INDEX | (Not in Annex VI of CLP Regulation 1272/2008) |
| EC No | 5 | EINECS – ELINCS - NLP | 202-465-7 |
| CAS No | 6 | Chemical Abstract Service number | 95-93-2 |
| Harmonised CLP classification | 7 | Human health risk-related classification | Not harmonised |
| Molar mass and conversion factor | 8 | [g/mol] and [ppm – mg/m$^3$] | 134.22<br>1 ppm = 5.52 mg/m$^3$ |
| **Key data / database** | | | |
| Key study, author(s), year | 9 | Critical study with lowest relevant effect level | |
| Read-across compound | 10 | Where applicable | Trimethylbenzenes |
| Species | 11 | Rat etc. / human | |
| Route/type of study | 12 | Inhalation, oral feed, etc. | |
| Study length | 13 | Days, subchronic, chronic | |
| Exposure duration | 14 | Hours/day, days/week | |
| Critical endpoint | 15 | Effect(s), site of | |
| Point of departure (POD) | 16 | LOAEC*L, NOAEC*L, NOEC*L, benchmark dose, etc. | POD/TAF in EU-LCI factsheet for trimethylbenzenes |
| POD value | 17 | [mg/m$^3$] or [ppm] or [mg/kg$_{BW}$×d] | 0.439 mg/m$^3$ |
| **Assessment Factors (AF)** | **18** | | |
| Adjustment for exposure duration | 19 | Study exposure hours/day, days/week | - |
| Study Length | 20 | sa→ sc→ c<br>*(R8-5)* | - |
| Route-to-route extrapolation factor | 21 | | - |
| Dose-response | 22 a | Reliability of dose-response, LOAEL → NOAEL | - |
| | 22 b | Severity of effect *(R 8-6d)* | - |
| Interspecies differences | 23 a | Allometric<br>Metabolic rate *(R8-3)* | - |
| | 23 b | Kinetic + dynamic | - |
| Intraspecies differences | 24 | Kinetic + dynamic<br>Worker - general population | - |
| AF (sensitive population) | 25 | Children or other sensitive groups | - |

| | | | |
|---|---|---|---|
| Other adjustment factors<br>Quality of whole database | 26 | Completeness and consistency<br>Reliability of alternative data *(R8-6 d,e)* | 2 |
| **Result** | | | |
| Summary of assessment factors | 27 | Total Assessment Factor (TAF) | 2 |
| POD/TAF | 28 | Calculated value (µg/m³ and ppb) | 219.5 µg/m³ and 44.38 ppb |
| Molar adjustment factor | 29 | Used in read-across | 1.117 (=134.22/120.19) |
| Rounded value | 30 | [µg/m³] | 250 |
| **Additional comments** | 31 | | |
| | | | |
| **Rationale section** | 32 | | |

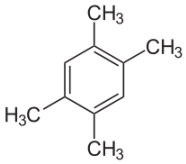
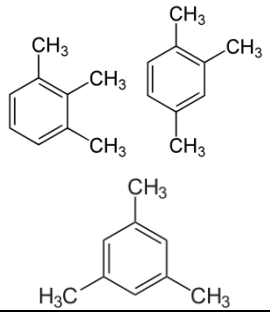
For 1,2,4,5-tetramethylbenzene, an acute inhalation study on rats and mice by Korsak et al. (1998) showed no lethal effects up to the highest test concentration (1200 mg/m³; 4 hrs). The results indicated some reduced pain perception, an effect similarly observed for trimethylbenzenes in the course of subchronic toxicity testing (see MAK documentation for trimethylbenzenes) and not unusual for organic solvents of such structure. Since no subchronic toxicity studies were available for tetramethylbenzene, Korsak et al. proposed an OEL of 25 mg/m³ derived from an RD 50 for sensory irritation, employing the Alary factor 0.03 which is a convention for many cases where no further specific effects are to be expected at concentrations close to the proposed OEL. Trimethylbenzenes have a MAK value in Germany of 100 mg/m³. This is four-fold higher than the OEL which Korsak et al. propose for tetramethylbenzene. Given the fact that no subchronic studies are available for the tetramethylbenzene, the lower OEL proposal appears to be a reasonable approach to take.

Trimethylbenzenes are quite rapidly metabolised to benzoic acid homologues and then conjugated with glycine (see MAK documentation). On the other hand, trimethylbenzenes also have the potential to accumulate in fat tissue, at least at higher dose levels, and this is probably important for the neurological effects observed both with this compound and with tetramethylbenzene in the acute study by Korsak et al. A similar metabolic profile may be assumed for the biotransformation of tetramethylbenzene. Accumulation of tetramethylbenzene in fat (and nerve) tissue should be assumed for higher doses, maybe even more than in the case of trimethylbenzenes.

Thus, derivation of an EU-LCI for tetramethylbenzene by read-across from trimethylbenzenes seems justified.

**Rationale for read-across**

- Data-poor compound: no adequate toxicological data for 1,2,4,5-tetramethylbenzene; *de novo* derivation of EU-LCI is not possible.
- Read-across candidate compounds for the starting value: within the chemical class of 'saturated aromatic hydrocarbons', trimethylbenzenes are the closest homologue with an EU-LCI value.
- Toxicological critical endpoints for homologue compound:
    - trimethylbenzenes: neurotoxicity and local effects on lungs.
- The key assumption underlying the read-across of the EU-LCI value from trimethylbenzenes to 1,2,4,5-tetramethylbenzene is that both compounds have a similar toxicity profile.
- The chemical structure and molecular weight of 1,2,4,5-tetramethylbenzene and trimethylbenzenes are listed in the table below:

| Compounds | Structure | MW [g/mol] | EU-LCI value |
|---|---|---|---|
| 1,2,4,5-Tetramethylbenzene |  | 134.22 | |
| Trimethylbenzenes |  | 120.19 | 450 µg/m$^3$ (*de novo* protocol)<br>Unrounded value: 439.29 µg/m$^3$ or 88.84 ppb |

- No cut-off rule in place: the difference in change length between the two homologue compounds is smaller than two CH2 groups per aliphatic chain.
- The EU-LCI Group considers that 1,2,4,5-tetramethylbenzene could be more potent than trimethylbenzenes. Due to the fourth methyl group, a higher accumulation of tetramethylbenzene in fat (and nerve) tissue than trimethylbenzenes is possible. These remaining quantitative uncertainties justify the use of an additional assessment factor (AF) of 2 for the quality of the whole database. The use of this additional AF in this case is an exception and will not be routine within the read-across approach.
- Thus, after molar weight conversion at 23 °C and 1 atm: EU-LCI 1,2,4,5-tetramethylbenzene = 439 µg/m$^3$ / 2 x 1.117 = 245 µg/m$^3$ → to be rounded to 250 µg/m$^3$.

**Sensory effects**

Acute respiratory sensory irritation was quantified by determining the decrease in respiratory rate in male Balb/c mice. 1,2,4,5-tetramethylbenzene depressed the respiratory rate and the concentration at which the respiratory rate was decreased to 50 % (RD50) was 838 mg/m$^3$ (153 ppm) (Korsak et al., 1998). Lowest observed adverse effect level (LOAEL) was calculated according to the (Kuwabara et al., 2007) algorithm (log RD50 = 1.16(log LOAEL) + 0.77) to 16.55 ppm (91 mg/m$^3$). Applying an AF of 5 for steepness (Nielsen et al., 2007) and a conservative AF of 10 for sensitivity, the estimated NOAEL value for tetramethylbenzene is 2 mg/m$^3$ for sensory irritation.

**References**

Korsak, Z.; Majcherek, W. and Rydzyński, K.: *Toxic effects of acute inhalation exposure to 1,2,4,5-Tetramethylbenzene (durene) in experimental animals*, International Journal of Occupational Medicine and Environmental Health, 1998, 11 (3), 267-272.

Kuwabara, Y.; Alexeeff, G.V.; Broadwin R. and Salmon A.G.: *Evaluation and Application of the RD50 for Determining Acceptable Exposure Levels of Airborne Sensory Irritants for the General Public*, Environ Health Perspec, 2007, 115, 1609-1616.

MAK documentation for Trimethylbenzenes, onlinelibrary.wiley.com/book/10.1002/3527600418/topics, 2001.

Nielsen, G.D., Wolkoff, P. and Alarie, Y.: *Sensory Irritation: Risk Assessment Approaches,* Regul Toxicol Pharmacol, 2007, 48, 6-18.