



Occupational Exposure Limits: Criteria Document for Manganese

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Purpose of criteria document

- Complete review of health, toxicological and other relevant properties of a chemical:
 - to allow the European Union (EU) Scientific Committee on Occupational Exposure Limits (SCOEL) to recommend values for occupational exposure limits (OELs) to the European Commission (EC)
- These OELs are either Indicative Occupational Exposure Limits Values (IOELVs) or Binding Limits Values (BLVs)
- Once agreed, they must be used in all member states

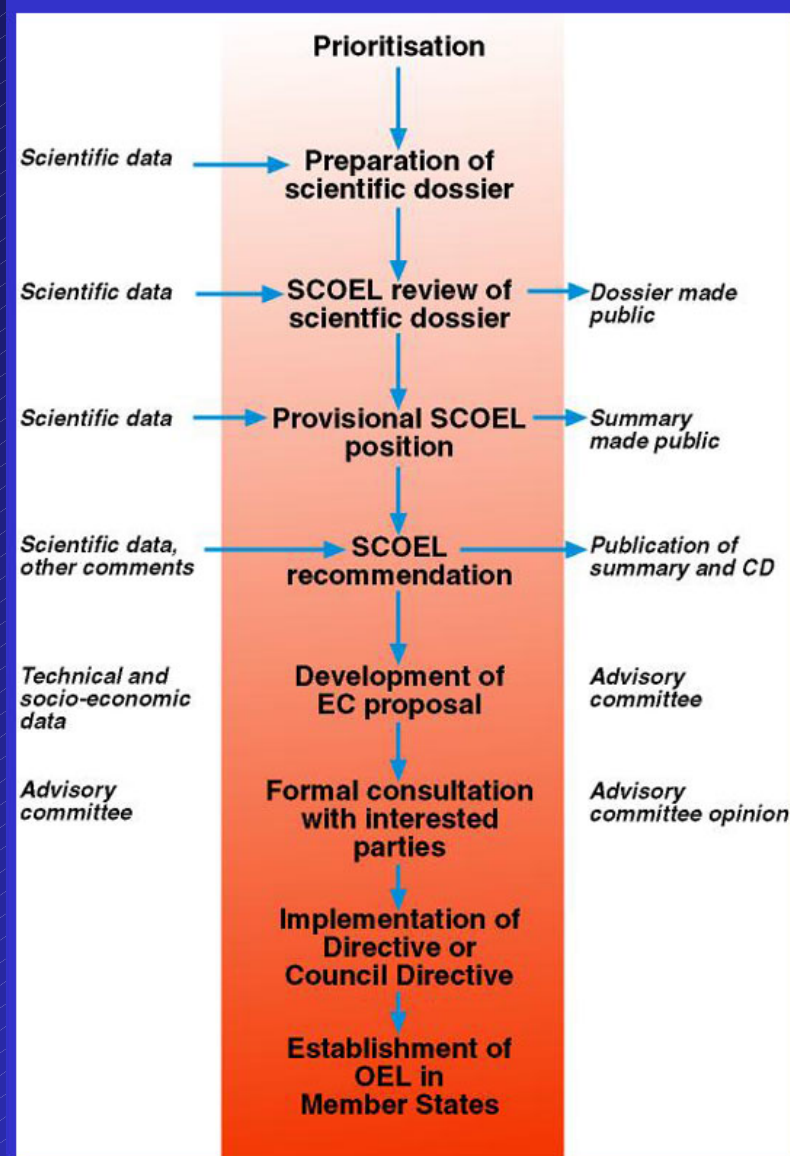
The team

- **Institute for Environment and Health**
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- **Institute of Occupational Medicine**
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Outline of criteria document

- Substance identification
- Chemical and physical properties
- Occurrence
- Production and use
- Measurement techniques and analytical methods
- Quantitative information on exposure and uptake
- Toxicology
- Knowledge gaps
- Vulnerability (Groups at extra risk)
- Existing occupational exposure limits
- Summary evaluation and recommendation for occupational exposure limits

Procedure for establishing European Union OELs (IOELV/BLV)



European indicative limit values



Why a criteria document on manganese?

- Manganese ore is an important commodity
- Manganese used in production of ferrous and non-ferrous alloys, including alloys essential to steel making, plus other industrial uses
- Historically, exposure associated with manganism — resembling idiopathic Parkinson's disease
- More recently concerns about subtle, non-clinical neurobehavioural/neurotoxicological effects
- Several countries are producing their own new OELs (e.g. USA)

Remit of criteria document on manganese

- Critical review of potential health effects of inorganic manganese compounds
- Critical review of supporting physicochemical, use and occupational exposure data
- Structure and content according to EC guidance on derivation and preparation of OELs¹ and on qualitative evaluation of human behavioural studies on neurotoxicity²

¹CEC (1992) Occupational Exposure Limits. Criteria Documents. Guidance Note (EUR 13776 EN); CEC (1999) Methodology for the Derivation of Occupational Exposure Limits: Key documentation (EUR 19253 EN); ²CEC (1997) Occupational exposure Limits: Criteria for the Qualitative Evaluation of Human Neurobehavioural Studies of Neurotoxicity (EUR 17390 EN)

Literature database

- Dec 2001(& Aug 2002): searches Medline (1966+), Embase (1974+), Toxfile (1966+)
- To identify articles on toxicity, carcinogenicity, teratogenicity, mutagenicity, health effects—for manganese and compounds
- Searches for exposure data on Medline, HSELine, CISDOC, NIOSHTIC, RILOX, EMBASE and in NIOSH and ACGIH publications
- Additional published/unpublished exposure data and reports from industry
- Bibliographic details of relevant review and original articles downloaded
 - >4000 titles identified
 - >800 references selected for review
 - 547 citations in final document

Industry sectors

Producer sectors

- Mining
- Production of manganese metal and metal alloys
- Chemical production of manganese-based chemicals

User sectors¹

- Steel production
- Other metal smelting processes
- Fabrication (including welding)
- Battery manufacture
- Agricultural products
- Pigments, paints and glass making

¹Iron & steel production 85–95% manganese market worldwide

Exposure metrics

- Interpretation of exposure studies must account for different exposure metrics and relationship between them
 - inhalable (e.g. by IOM sampler), respirable, total (e.g. by 37mm cassette)
- Suggested ratios
 - inhalable: total 1.2–3.0:1
 - respirable:total 0.1–0.5:1
- Important in proposing OELs

Typical occupational exposures

- **Mining**
 - Well controlled SA
AM total $0.21\text{mg}/\text{m}^3$
 - Poorly controlled Iran
AM total $114\text{mg}/\text{m}^3$
- **Metal/alloy**
 - Well controlled USA
GM total $0.11\text{mg}/\text{m}^3$
 - Alloy, poorly controlled
GM inhal. $2.43\text{mg}/\text{m}^3$
- **Chemical**
 - Well controlled USA
GM total $0.16\text{mg}/\text{m}^3$
 - Typical Belgium
GM total $0.94\text{mg}/\text{m}^3$
- **Steel-making**
 - Typical Sweden
AM total $0.41\text{mg}/\text{m}^3$
- **Other metal**
 - Typical Denmark
AM total $0.039\text{mg}/\text{m}^3$
- **Welding**
 - Typical UK
AM total $0.36\text{mg}/\text{m}^3$
- **Battery**
 - Typical Europe
GM total $0.95\text{mg}/\text{m}^3$

Key health effects

- Manganese exposure associated, in some studies, with adverse respiratory and cardiovascular effects (neither expected at inhalable exposures less than $1\text{mg}/\text{m}^3$)
- No strong evidence that manganese is an irritant except at high exposure levels
- Limited data do not suggest manganese has a strong sensitising potential
- Neurological effects of manganese are considered the major concern for the establishment OELs

Cancer

Data on carcinogenicity, mutagenicity and genotoxicity are inconclusive and inadequate to establish a definitive position on the carcinogenicity of manganese.

Reproductive effects

There is little evidence for the reproductive or developmental toxicity of manganese.

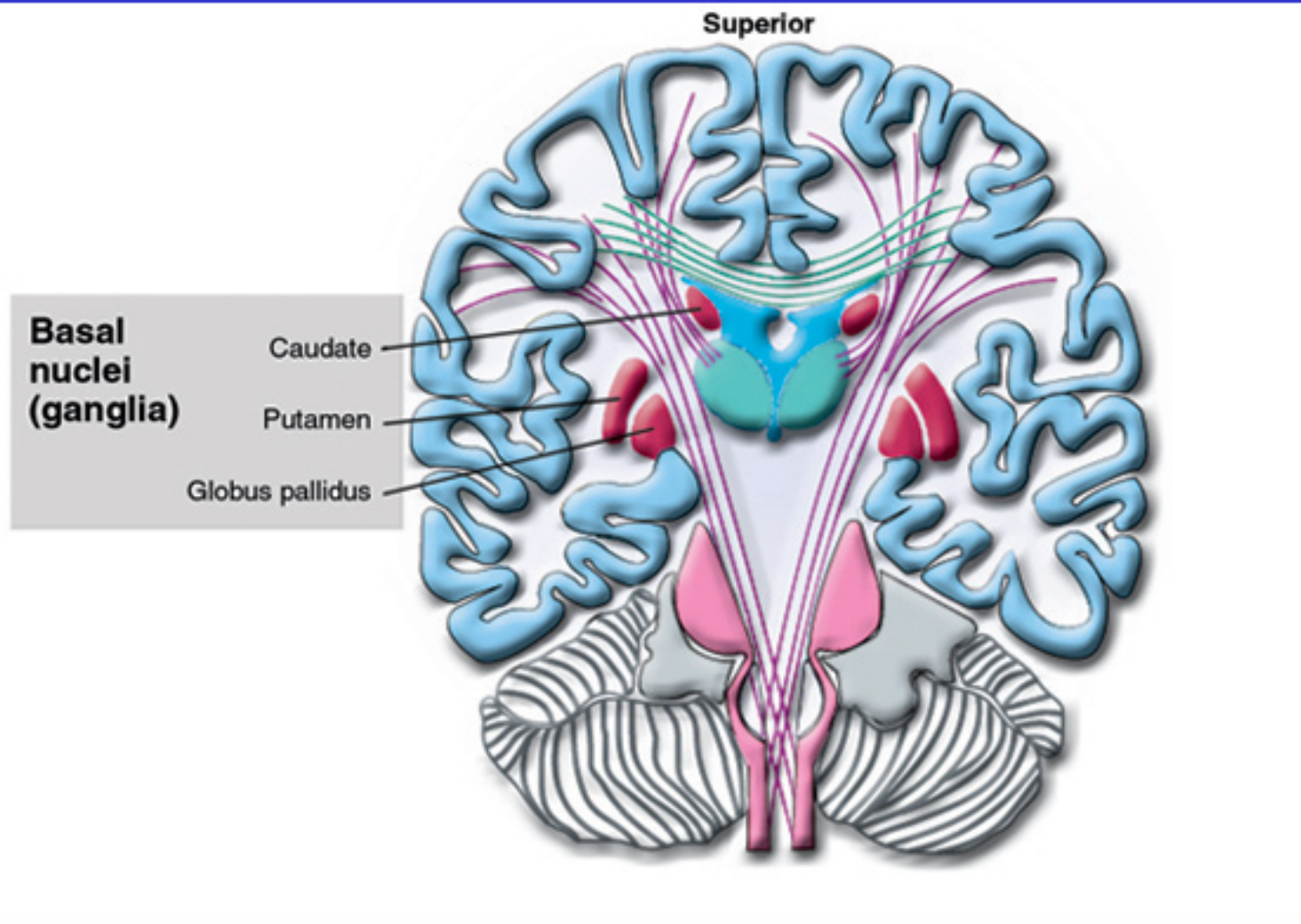
Neurotoxicity

- Substantial literature on effects of manganese exposure on human nervous system
- High exposures can result in severe neurotoxic signs and symptoms resembling idiopathic Parkinson's disease
- Syndrome (may also include psychiatric effects) — 'Manganism'
- Clinical symptoms of manganism (movement disorders, neurological dysfunction) generally only at exposures above $\sim 5\text{mg}/\text{m}^3$

Non-clinical neurological effects

- Recent studies on lower occupational exposures to manganese have reported less severe, subtle, non-clinical neurobehavioural/neurotoxicological effects
 - Deterioration in motor function and coordination
 - May constitute manganese-induced changes in same area of brain as manganism
i.e. basal ganglia, particularly globus pallidus

Sites of manganese accumulation and action in brain



Relevance of neurobehavioural motor effects

- Consistent with manganism
 - Plausible that mild effects of relevance to later clinical disease
- Less likely to be affected by intellectual capacity or social class than other neurological effects
 - Thus findings of association with manganese relatively robust in face of possible confounding factors
 - Motor activity tests positive rather than intellectual tests

Epidemiological studies of neurobehavioural effects

- Studies on subtle neurobehavioural effects evaluated based on methodological quality and quality of exposure data
- Of 28 studies considered, 3 identified as basis for setting OELs
- 3 Further studies provide information on possible progression and reversibility of effects

Key epidemiology studies

- Roels *et al.* (1992), Belgian battery factory, subtle neurological effects observed in about 15% of those exposed to an average respirable level of 0.2 (GM) mg/m³
- Gibbs *et al.* (1999), US manganese metal production, no established effect at average respirable level of 0.04 (GM), 0.07 (AM) mg/m³
- Myers *et al.* (2002) study, SA manganese ore mines, no effect at average total exposure of 0.2 (AM) mg/m³, equivalent to respirable exposure of 0.04–0.08 mg/m³

Progression and reversibility

- Lucchini *et al.* (1999) confirmed motor function changes in a group of ferroalloy workers examined in earlier study but found no evidence of progressive deterioration (exposure to manganese reduced in the interim period)
- Crump & Rousseau (1999) little or no evidence of progression of neurobehavioral effects in chemical production workers
- Roels *et al.* (1999) some limited evidence for reversibility of adverse effects in battery workers re-tested following 8-year period during which exposure reduced

Experimental toxicity

- Many of effects observed in humans also demonstrated in experimental (animal) models,
- Important inter-species differences in toxicokinetics and toxicodynamics
- Data from animal studies on neurotoxicity broadly supportive of findings in humans
- Rodent more sensitive than humans to manganese
- Inhalation LOAEL $3.75\text{mg}/\text{m}^3$ (neurobehavioural & neurochemical effects in rats)
Uncertainty factor 10 (conversion LOAEL to NOAEL) \times 3 (human individual variation)
gives exposure limit of $\sim 0.125\text{mg}/\text{m}^3$

Derivation of OELs

- Most sensitive endpoint is neurological (i.e. systemic effect)
- Respirable fraction better indicator of systemic availability
- Large proportion of inhalable fraction would enter gastrointestinal (GI) tract but GI absorption is low
- Thus, the most appropriate measure for standard is respirable dust level
- For processes where respirable:inhalable ratio is low, subsidiary inhalable standard proposed

Basis for recommendations

- OEL for respirable manganese, based on 3 key studies on motor neurobehavioural changes
- No uncertainty factors applied as the recommendation is based on human data and on non-clinical endpoints only detected using specific test procedures
- Appears that motor effects are neither all reversible nor progress to clinical disease
- Supplementary inhalable limit for scenarios where GI absorption subsequent to inhalation may not be insignificant

Recommendations for OELs

- For inorganic forms of manganese, limiting exposure to 0.1 mg/m³ respirable manganese will prevent most workers from developing the subtlest detectable adverse effect, that is, motor neurobehavioral changes.
- A supplementary limit of 0.5 mg/m³ inhalable manganese is recommended as a safeguard, in case the gastrointestinal route, subsequent to inhalation, is not insignificant.
- In making these recommendations it is noted that limited evidence is available to evaluate effects over a working lifetime. At the levels recommended there is no foreseen problem with measurement in an occupational setting. Neither a short-term exposure limit nor a skin notation is needed.