manganese, arterial plaque, preclinical and clinical studies in reputable journals

Manganese sits in an awkward middle ground: there is intriguing preclinical work suggesting both protective and therapeutic effects on plaque biology and lipids, but essentially no human interventional data targeting atherosclerotic plaque, and some epidemiology hinting at cardiovascular risk at higher systemic exposure.[1] [2] [3]

Mechanistic and preclinical data

- **Mn-SOD and vascular protection.** Manganese is the metal cofactor for mitochondrial superoxide dismutase (Mn-SOD), and increased Mn-SOD expression can prevent atherosclerosis development and unstable plaque formation in experimental systems. Mn-SOD activity is increased in the intima of atherosclerotic arteries, and oxidized LDL is a key upstream driver of both macrophage damage and plaque progression.[4]
- **"Manganese therapy" in mice.** A 2023 Life Metabolism paper used dietary $MnCl_2$ titration in ApoE-/- murine models of hyperlipidemia, producing marked, dose-dependent lipid lowering and plaque regression.[5] [1]
    - After 16 weeks of pathogenic induction, 12 weeks of Mn^{2+} in drinking water (0.2–1 g/L) led to up to ~75% reduction in aortic Oil Red O–positive plaque area at the highest dose, versus a ~15% plaque increase in vehicle controls.[1] [5]
    - Imaging (FMT and 3D magnetic particle imaging) plus en-face aortic analysis showed near-disappearance of signals from plaque-targeted nanoparticles in high-dose Mn^{2+} animals, consistent with reversal of established, likely unstable plaques.[5] [1]
    - The authors emphasize this as a proof-of-concept that "manganese-based therapy" can reverse plaques via intensive lipid lowering in mice, not a ready-for-human dosing paradigm.[1] [5]

Imaging and nano-construct work (plaque biology, not systemic therapy)

- **Mn-based molecular imaging of plaque.** Several groups have used manganese as a paramagnetic payload in MR contrast agents that target components of atherosclerotic plaques.
    - Carotid endarterectomy specimens show paramagnetic manganese within plaques, linked to processes such as macrophage apoptosis and Mn-SOD upregulation.[4]
    - Manganese-containing micelles that bind oxidized LDL are taken up by lesional macrophages; intracellular Mn release markedly increases MR relaxivity, enhancing plaque signals on T1-weighted imaging in preclinical models.[6]

    - Mixed manganese/gadolinium nano-contrast agents (MnOL-Gd nanocolloids) targeting αvβ3 integrins have been used to image plaque neovascularization in cholesterol-fed rabbits, demonstrating specific enhancement of neovessels and enabling 3D reconstruction of neovascular distribution as a putative plaque-risk biomarker.[7]
- These constructs treat manganese as a **local imaging payload** with potential theranostic angles, rather than as systemic Mn supplementation intended to modify human plaque burden.[6] [7]

Human observational and physiological data

- **Blood manganese and hemodynamics.** A 2023 study in older adults found a non-linear positive association between blood manganese (bMn) and 24-h brachial and central blood pressure and pulse-wave velocity (PWV), with a more linear association for nighttime pressures. Higher bMn quintiles were associated with modestly higher systolic and diastolic pressures and greater PWV, suggesting manganese exposure might contribute to cardiovascular risk in this population.[2]
- **Dietary manganese intake and CVD mortality.** A large Japanese cohort reported that higher dietary Mn intake was associated with lower mortality from total stroke and ischemic stroke; participants in the highest Mn quintile had a significantly reduced hazard ratio for stroke mortality compared with the lowest quintile. This suggests a U-shaped or context-dependent relationship between manganese nutrition and vascular outcomes, and may be confounded by overall dietary patterns.[3]
- **Acute Mn infusion safety (cardiac imaging).** In a cardiac manganese-enhanced MRI study using manganese dipyridoxyl diphosphate, 78 infusions (10-min) were completed without significant changes in ECG, heart rate, or blood pressure, indicating that short, controlled Mn exposure in chelated form can be hemodynamically well tolerated in humans. This informs imaging safety more than chronic plaque biology.[8]

Cardiovascular toxicity and exposure limits

- High-dose intravenous Mn (5–10 mg Mn/kg) in animal models acutely decreases heart rate and blood pressure and prolongs PR and QRS intervals, reflecting direct cardiac conduction effects at pharmacologic exposure.[2]
- Chronic manganese overexposure is better known for neurotoxicity, but the blood pressure and arterial stiffness data above suggest there may be cardiovascular penalties at higher bMn even below overt toxicity thresholds.[2]

Clinical translation status

- There are **no human randomized controlled trials** where manganese supplementation or restriction is used specifically as a therapy to regress atherosclerotic plaque or reduce clinical atherosclerotic events.[1] [2]
- The strongest “therapeutic” evidence is the murine manganese-titration work, which shows robust plaque regression tied to lipid lowering but at exposure levels and with biology that may not be directly scalable to humans.[5] [1]

- Mn-based agents are progressing mainly in the context of **imaging and theranostics** (plaque-targeted MR contrast, nanozymes), often in combination with other metals or drugs, and remain preclinical.[9] [7] [6]

If you want, I can pull specific dosing details, administration routes, and lipid/plaque effect sizes from the murine manganese-therapy paper into a compact table to see where it might intersect (or conflict) with plausible human exposure ranges.

⁂

I can pull specific dosing details, administration routes, and lipid/plaque effect sizes from the murine manganese-therapy paper into a compact table to see where it might intersect (or conflict) with plausible human exposure ranges.

Here is a compact view of the key dosing, routes, and effect sizes from the murine manganese-therapy work, plus how they sit relative to plausible human exposure ranges.

Murine manganese therapy details

Core design (hyperlipidemia/atherosclerosis model)

Feature	Details	Source
Species/model	Mouse, atherosclerosis induced by high-fat Western diet with controlled Mn content	[16] [17] [18] [19]
Pathogenic phase	4 months on Mn-deficient Western diet + 0.02 g/L Mn^{2+} in drinking water (≈“normal” Mn supply)	[16] [17]
Therapeutic phase start	After confirmation of hyperlipidemia and atherosclerotic plaque development	[16] [17] [18]
Therapeutic groups	Control (0 g/L), Mn^{2+} in drinking water at 0.2, 0.6, or 1 g/L	[16] [17]
Administration route	Continuous oral exposure via drinking water ($MnCl_2$ providing Mn^{2+})	[16] [17]
Duration of therapy	12 weeks of Mn^{2+} titration during therapeutic phase	[16] [17] [19]

Lipids and plaque outcomes in mice

Parameter	Effect at highest Mn^{2+} dose (1 g/L in water)	Dose–response notes	Source
Plasma triglycerides	Mn^{2+} supplementation restored or normalized plasma TG in hypolipidemic LKO mice in a clear dose-dependent manner (0.02 → 0.2 → 1 g/L).[16]	0.02 g/L ≈ baseline nutrition; 0.2 and 1 g/L produced graded increases in circulating lipids.[16] [17]	[16] [17]

Parameter	Effect at highest Mn^{2+} dose (1 g/L in water)	Dose–response notes	Source
Hyperlipidemia in AS model	In high-fat diet model, higher Mn^{2+} dosing reduced pathological hyperlipidemia, i.e., intensive lipid lowering in hyperlipidemic animals. [18] [19]	Authors frame Mn as a "signal" to tune hepatic lipid export via COPII, giving bidirectional control depending on baseline state. [18] [19]	[18] [19]
Aortic plaque (Oil Red O)	Ex vivo en-face analysis: 1 g/L Mn^{2+} enabled "substantial reversal" of atherosclerotic plaques formed over the 4-month pathogenic phase; remaining Oil Red O signal interpreted as smaller, more stable plaques. [16] [17] [19]	Vehicle controls showed continued plaque progression over same period, while 0.2 and 0.6 g/L groups showed intermediate plaque reduction. [16] [17]	[16] [17] [19]
Imaging readouts	Multimodal imaging (FMT, 3D MPI with plaque-targeted tracer) showed near-disappearance of plaque-associated tracer signal in 1 g/L group, concordant with histologic plaque regression. [16] [19]	Imaging signal decreased in a dose-dependent fashion, paralleling histology. [16]	[16] [19]
Safety in mice	Authors report "no apparent toxicity" with dietary Mn titration across doses used. [18]	This is based on murine clinical observations and gross pathology; not directly translatable to human neurotoxicity thresholds. [18]	[18]

Additional murine $MnCl_2$ atherosclerosis data

Study	Regimen	Main vascular/cardiac findings	Source
$MnCl_2$ in $ApoE^{-/-}$ mice (cardiac remodeling)	Oral $MnCl_2$ in high-fat diet $ApoE^{-/-}$ mice; specific mg/kg not in abstract but delivered chronically. [20]	Reduced spontaneous supraventricular arrhythmia, improved systolic function, inhibited aortic plaque formation, decreased inflammatory cell infiltration and fibrosis, effects described as "lipid metabolism-independent." [20]	[20]

Intersection with human exposure ranges

We obviously cannot scale 0.2–1 g/L Mn^{2+} in mouse drinking water directly to humans, but it is useful to contrast with current human intake guidance.

Human intake benchmarks

Parameter	Value / comment	Source
RDA (men ≥19 y)	2.3 mg/day Mn	[21]
RDA (women ≥19 y)	1.8 mg/day Mn	[21]
US/NIH UL (adults)	11 mg/day total Mn from all sources	[22]
EFSA "safe intake" (adults)	8 mg/day total Mn from all sources (no formal UL possible with current data)	[23]

Parameter	Value / comment	Source
Observational BP/PWV data	Higher blood Mn levels in older adults associate with higher 24-h brachial and central BP and higher pulse-wave velocity, with non-linear but overall positive relationship.[24]	[24]
Stroke mortality vs dietary Mn (Japan)	Highest quintile of dietary Mn intake associated with lower ischemic stroke mortality vs lowest quintile in a large cohort.[25]	[25]

Qualitative comparison: murine vs human exposure

- The murine therapeutic concentrations (0.2–1 g/L Mn^{2+} in water) are **orders of magnitude** above normal human dietary intake when naively converted to mg/L, even before accounting for species-specific differences in water consumption per kg and Mn handling. [16] [17] [18]
- In mice, these levels were sustained for 12 weeks and described as having no apparent toxicity; however, human guidance (NIH, EFSA) flags uncertainty around chronic Mn safety and keeps adult "safe" intake tightly in the single-digit mg/day range, with concern about neurotoxicity and, more recently, blood-pressure/arterial-stiffness associations at higher systemic levels.[23] [22] [24]
- Put differently: the **therapeutic window** exploited in the murine work to drive intensive lipid lowering and plaque regression almost certainly lies well beyond what is currently considered acceptable chronic intake in humans, pending far more granular toxicology and kinetic data.[18] [16] [23]

If you'd like, the next step would be to do a rough-and-ready allometric scaling (using typical mouse water intake per kg) to estimate ballpark daily Mn doses (mg/kg/day) in the 0.2–1 g/L arms, then overlay those against current human mg/kg/day equivalents at the 8–11 mg/day "safe" range.

⁂

the next step would be to do a rough-and-ready allometric scaling (using typical mouse water intake per kg) to estimate ballpark daily Mn doses (mg/kg/day) in the 0.2–1 g/L arms, then overlay those against current human mg/kg/day equivalents at the 8–11 mg/day "safe" range.

Using standard mouse water-intake defaults plus regulatory human reference values, the murine "manganese therapy" doses land orders of magnitude above current human "safe" ranges on an mg/kg basis.[33] [34] [35]

Step 1 – Estimate murine Mn doses (mg/kg/day)

Assumptions

- Adult mouse body weight: 25 g (0.025 kg) – typical for C57BL/6J.[35]
- Daily water intake: 15 ml/100 g/day ≈ 15 ml per 100 g, i.e. 0.15 ml/g/day.[36]
  - For 25 g mouse → 0.15 × 25 ≈ 3.75 ml/day, consistent with independent estimates of 3.9–8.2 ml/mouse/day and a strain mean ≈5.8 ml/mouse/day.[37] [38]
- Mn^{2+} concentrations: 0.2, 0.6, 1 g/L = 200, 600, 1000 mg/L Mn^{2+} in drinking water.[35]

Approximate daily Mn dose for a 25 g mouse:

Water Mn^{2+} (g/L)	Mn conc (mg/L)	Daily water (ml)	Daily Mn (mg/day)	Mn dose (mg/kg/day)
0.2	200	3.75	0.75	30
0.6	600	3.75	2.25	90
1.0	1000	3.75	3.75	150

So the therapeutic range in the Life Metabolism study is roughly **30–150 mg/kg/day** Mn^{2+} for 12 weeks, with the ~150 mg/kg/day arm driving ≈75% plaque-area reduction vs baseline in the robust hyperlipidemia model.[35]

Step 2 – Human reference doses (mg/kg/day)

Key human benchmarks:

- Typical dietary intake in adults in Germany ≈2.8 mg/day for a 70-kg person → about 0.04 mg/kg/day.[39]
- US IOM/ATSDR: adult tolerable upper intake level (UL) 11 mg/day, interpreted as ≈0.16 mg/kg/day for a 70-kg adult.[34]
- EPA oral reference dose (RfD) for total manganese intake: 0.14 mg/kg/day (~10 mg/day for 70-kg adult).[40] [34]

Approximate mg/kg at 70 kg:

Human Mn intake	Total (mg/day)	Mn dose (mg/kg/day)
Typical diet (Germany)	2.8	0.04
IOM UL	11	0.16
EPA RfD	10	0.14

Step 3 – Overlay murine vs human mg/kg/day

Compare approximate mg/kg/day:

Category	Mn dose (mg/kg/day)	Notes
Mouse “low therapy” (0.2 g/L)	~30	Mn^{2+} in water, 12 weeks.[35] [36]

Category	Mn dose (mg/kg/day)	Notes
Mouse “mid therapy” (0.6 g/L)	~90	Strong lipid and plaque effects.[35]
Mouse “high therapy” (1.0 g/L)	~150	≈75% reduction in plaque area.[35]
Human typical diet	~0.04	Average German adult.[39]
Human UL (IOM)	~0.16	11 mg/day, 70-kg adult.[34]
Human RfD (EPA)	~0.14	10 mg/day, 70-kg adult.[34] [40]

On a **per-kg basis**, the effective mouse doses are approximately:

- Low therapy vs human UL: 30 / 0.16 ≈ 190-fold higher.
- High therapy vs human UL: 150 / 0.16 ≈ 900-fold higher.

Given that human UL/RfD levels already sit close to intakes where subtle neurological and cardiovascular effects become a concern, there is currently **no plausible path** to simply “scale down” the murine manganese-therapy regimen to humans without running far beyond accepted chronic exposure limits.[41] [34] [40]

⁂

What are safe Mn exposure limits mg/kg/day for humans

Key agencies converge on a “safe” chronic oral exposure band around 0.03–0.16 mg/kg/day for adults, depending on whether you look at nutritional needs or toxicology-based limits.[49] [50]

Core numeric values (adults, oral exposure)

- **Adequate intake (AI/RDA level)**
  - Men: 2.3 mg/day → ≈0.033 mg/kg/day for 70-kg adult.[51] [49]
  - Women: 1.8 mg/day → ≈0.026 mg/kg/day for 70-kg adult.[49] [51]
- **IOM / FNB tolerable upper intake level (UL)**
  - UL: 11 mg/day for adults.[51] [49]
  - As mg/kg/day (70-kg reference): 11 / 70 ≈ **0.16 mg/kg/day**.[50] [49]
- **US EPA oral reference dose (RfD)**
  - RfD: **0.14 mg/kg/day** from all oral sources (food, water, soil).[52] [49]
  - EPA recommends a modifying factor of 1 if Mn is in food, 3 if primarily in water/soil, reflecting higher concern for waterborne Mn.[49]
- **ATSDR interim guidance (oral)**
  - ATSDR endorses using **0.16 mg/kg/day** as an interim oral guidance value, explicitly derived from the adult UL of 11 mg/day.[50]
- **EFSA “safe level of intake” (no formal UL)**

- Adults: 8 mg/day total Mn from all dietary sources.[53]
- 8 mg/day at 70 kg ≈ **0.11 mg/kg/day**, but EFSA stresses this is a pragmatic safe-intake level, not a toxicology-anchored UL.[53]

Practical takeaway

For a typical 70-kg adult, current regulatory and nutritional guidance places **chronic oral Mn exposure** as:

- Nutritional "need" band: roughly **0.03 mg/kg/day**.
- Toxicology-bounded "not likely to cause harm" band: about **0.11–0.16 mg/kg/day** (≈8–11 mg/day).[50] [53] [49]

The murine "manganese therapy" doses we estimated earlier (≈30–150 mg/kg/day) sit **hundreds-fold above** these human mg/kg/day values, which is why they cannot be naively translated to human chronic intake.

⁂

How is a SOD2 genetic decency related to manganese

SOD2 encodes the mitochondrial **manganese** superoxide dismutase (MnSOD), so any SOD2 deficiency is directly a problem of using manganese as an antioxidant cofactor inside mitochondria.[64] [65] [66]

Core relationship

- The SOD2 gene makes MnSOD, which is a tetrameric mitochondrial enzyme that binds one manganese ion per subunit and converts superoxide O_2^- to hydrogen peroxide and oxygen.[65] [66] [64]
- Because manganese is the essential catalytic metal, a SOD2 deficiency (loss-of-function mutation, low expression, or mis-targeting variant) effectively creates a **functional "manganese-SOD" deficiency** even if total body manganese status is normal.[67] [64] [65]

Types of "SOD2 deficiency" and manganese

- **Loss-of-function / low-activity variants.** Common polymorphisms such as Val16Ala alter mitochondrial targeting and/or activity of MnSOD, with the Val variant showing about 30–40% lower enzymatic activity and therefore less efficient use of manganese to detoxify superoxide.[68] [69] [67]
- **Complete or severe genetic deficiency.** Experimental models with reduced Sod2 expression show marked mitochondrial oxidative stress and can develop cardiomyopathy and neurodegeneration, again not because manganese is absent, but because the manganese-dependent enzyme is missing or inadequate.[70] [64] [65]

- **Cofactor loading vs global Mn status.** In yeast and cell models, impaired Mn delivery to SOD2 (e.g., MTM1 defects) leaves SOD2 largely inactive even when mitochondrial manganese content is normal; high manganese supplementation can rescue SOD2 activity, indicating that SOD2 "deficiency" can also arise from **manganese not being correctly inserted** into the SOD2 polypeptide.[71] [72]

Clinical/physiologic implications

- SOD2/MnSOD is a first-line mitochondrial defense against reactive oxygen species, so SOD2 deficiency increases superoxide levels, shifts the balance between superoxide and hydrogen peroxide, and is linked to conditions such as idiopathic cardiomyopathy, premature aging phenotypes, and some cancers.[69] [65] [70]
- In that context, manganese is not just another trace element; it is the **obligate cofactor** for SOD2, so SOD2 genetic status determines how effectively any given manganese status translates into actual antioxidant protection at the mitochondrial level.[73] [74] [64]

⁂

would supplementing manganese be beneficial for this condition

Evidence is very limited, and for someone with a true SOD2 (MnSOD) genetic deficiency there is **no clear proof** that manganese supplementation is beneficial, while there is clear potential for harm at higher intakes.

What we know mechanistically

- SOD2 encodes mitochondrial MnSOD, and this enzyme absolutely requires manganese as its cofactor to detoxify superoxide.[79] [80]
- In cell and yeast models where SOD2 protein is present but **poorly loaded with Mn** (e.g., MTM1 transporter defects), raising manganese availability can restore SOD2 activity by better metal loading of the enzyme.[81] [82]
- In senescent human fibroblasts in vitro, adding nanomolar Mn^{2+} to culture media increased SOD2 activity and reduced superoxide generation, suggesting Mn-replete conditions improve SOD2 function when the enzyme itself is intact.[83] [84]

Why this does not automatically justify oral Mn supplements

- Most human "SOD2 deficiency" states are due to **gene variants** (such as Val16Ala) that impair mitochondrial targeting or enzyme amount, not simple manganese lack; giving more Mn cannot fix the mis-targeted or missing enzyme.[85] [86] [87]
- Regulatory agencies set chronic oral Mn guidance for adults around 0.11–0.16 mg/kg/day (≈8–11 mg/day for 70 kg) because higher chronic exposure is linked to neurotoxicity and possibly higher blood pressure and arterial stiffness.[88] [89] [90]
- Epidemiologic data on cardiovascular endpoints are mixed (some data suggest higher Mn exposure associates with higher blood pressure, others see inverse associations using

urinary Mn), so pushing intake above current "safe" levels to try to drive more SOD2 activity is not risk-free.[91] [88]

Practical implication for someone with SOD2 issues

- Keeping manganese intake in the **normal dietary range** (around 1.8–2.3 mg/day, ≈0.03 mg/kg/day) is reasonable to avoid functional Mn deficiency that could further limit SOD2 activity.[92] [93]
- Going above established upper limits (about 8–11 mg/day for adults) specifically to "treat" a SOD2 polymorphism or partial deficiency currently lacks clinical trial support and carries potential neurological and cardiovascular risks.[89] [90] [88]
- If there is a documented SOD2 mutation or suspected mitochondrial disorder, any consideration of Mn supplementation beyond diet should be done only in a research or specialist setting, with monitoring and within existing intake limits.

If you tell me whether you're talking about a known SOD2 variant (e.g., Val16Ala on genetic testing) vs a suspected mitochondrial problem, I can tailor how to think about diet vs supplements and what testing or specialist input would make sense.

⁂

Optimal Mn dose to boost SOD2 without toxicity

There is no single "optimal" manganese dose defined for boosting SOD2 in humans; the only defensible target today is to stay replete (around the RDA) and not exceed established upper-intake limits.

What lab data show on SOD2 and Mn

- In senescent human fibroblasts in vitro, adding **60–180 nM Mn^{2+}** to culture medium progressively increased SOD2 activity and reduced superoxide generation, with Km values for Mn^{2+} in the low-tens of nanomolar range.[101]
- In yeast and other cell models, SOD2 activity can be restored by raising manganese in the local milieu when the problem is poor Mn loading of the enzyme, not an absence of SOD2 protein.[102] [103]
- These experiments tell us that MnSOD is very **sensitive to local Mn at nanomolar–micromolar levels** in mitochondria, but they do not translate directly into safe oral doses in people.[104] [101]

Human intake levels that are considered safe

For adults:

- **Adequate intake / RDA:** about **2–3 mg/day** total Mn, ≈0.03–0.04 mg/kg/day for a 70-kg adult. [105] [106]
- **Upper-intake / guidance band:**

- IOM/US NIH UL: **11 mg/day** (≈0.16 mg/kg/day) as the maximum daily intake unlikely to cause harm in almost all adults.[107] [105]
- EFSA "safe level of intake": **8 mg/day** (≈0.11 mg/kg/day) from all dietary sources; above this, risk from extra Mn (supplements/fortified foods) is unknown.[108] [106]

Neurotoxicity and possible increases in blood pressure and arterial stiffness are the main concerns with higher chronic exposure.[109] [110]

Putting this together for "boosting SOD2"

- **No human trials** define a specific supplemental Mn dose that increases SOD2 activity in vivo while proving long-term safety.
- Cell data support the idea that **marginal Mn deficiency** can limit SOD2, and correcting that deficiency helps; they do *not* justify large pharmacologic doses.[101] [104]
- The most evidence-aligned approach is:
  - Ensure Mn intake is at least in the **RDA range** (roughly 2–3 mg/day from food or modest supplements).[106] [105]
  - Avoid routinely exceeding about **8–11 mg/day total** (all sources combined), because that moves into a band where safety is uncertain or concerns emerge.[108] [105] [109]

So, the best current answer is that "optimal" intake for SOD2 support is **normal replete intake (around 2–3 mg/day)**, staying **below 8–11 mg/day total**, and there is no validated higher dose that boosts SOD2 enough to outweigh toxicity risks.

⁂

1. https://pmc.ncbi.nlm.nih.gov/articles/PMC11749556/
2. https://www.sciencedirect.com/science/article/abs/pii/S0013935123004176
3. https://www.jstage.jst.go.jp/article/jat/advpub/0/advpub_63195/_pdf
4. https://pmc.ncbi.nlm.nih.gov/articles/PMC5203874/
5. https://academic.oup.com/lifemeta/article/2/6/load040/7330705
6. https://radiologykey.com/molecular-mr-imaging-of-atherosclerosis/
7. https://pmc.ncbi.nlm.nih.gov/articles/PMC4720435/
8. https://www.nature.com/articles/s41598-023-29591-z
9. https://advanced.onlinelibrary.wiley.com/doi/10.1002/advs.202304294
10. https://www.eurekalert.org/news-releases/1006736
11. https://www.sciencedirect.com/science/article/pii/S0735109714010882
12. https://www.dovepress.com/recent-advances-in-nanozymes-for-the-treatment-of-atherosclerosis-peer-reviewed-fulltext-article-IJN
13. https://medicalxpress.com/news/2023-11-manganese-bullet-cardiovascular-disease-potential.html
14. https://www.nature.com/articles/s41598-018-21893-x
15. https://pmc.ncbi.nlm.nih.gov/articles/PMC11017846/

16. https://pmc.ncbi.nlm.nih.gov/articles/PMC11749556/
17. https://academic.oup.com/lifemeta/article/2/6/load040/7330705
18. https://pubmed.ncbi.nlm.nih.gov/39872857/
19. https://pmc.ncbi.nlm.nih.gov/articles/PMC11247199/
20. https://pubmed.ncbi.nlm.nih.gov/33451751/
21. https://nutritionsource.hsph.harvard.edu/manganese/
22. https://ods.od.nih.gov/factsheets/Manganese-Consumer/
23. https://www.efsa.europa.eu/en/plain-language-summary/scientific-opinion-tolerable-upper-intake-level-manganese
24. https://www.sciencedirect.com/science/article/abs/pii/S0013935123004176
25. https://www.jstage.jst.go.jp/article/jat/advpub/0/advpub_63195/_pdf
26. https://academic.oup.com/lifemeta/article-pdf/2/6/load040/57048628/load040.pdf
27. https://www.sciencedirect.com/science/article/pii/S0955286326000392?dgcid=rss_sd_all
28. https://www.biorxiv.org/content/10.1101/2024.12.04.626925v1.full-text
29. https://www.science.org/doi/10.1126/sciadv.adv2485
30. https://pmc.ncbi.nlm.nih.gov/articles/PMC11514794/
31. https://medicalxpress.com/news/2023-11-manganese-bullet-cardiovascular-disease-potential.html
32. https://www.sciencedirect.com/science/article/pii/S2090123224006271
33. https://www.sciencedirect.com/science/chapter/bookseries/pii/B9780444818713500199
34. https://www.atsdr.cdc.gov/toxprofiles/tp151-c8.pdf
35. https://pmc.ncbi.nlm.nih.gov/articles/PMC11749556/
36. https://animal.ncku.edu.tw/p/412-1130-22971.php?Lang=en
37. https://www.mcgill.ca/research/files/research/417-_food_and_water_restriction_in_rodents.pdf
38. https://pmc.ncbi.nlm.nih.gov/articles/PMC1397713/
39. https://pubmed.ncbi.nlm.nih.gov/31216097/
40. https://www.industrialchemicals.gov.au/sites/default/files/Manganese_Human health tier II assessment.pdf
41. https://www.sciencedirect.com/science/article/abs/pii/S0013935123004176
42. https://www.urmc.rochester.edu/MediaLibraries/URMCMedia/animal-resource/forms/documents/Interpreting-Mouse-Chow-Supply-and-Drinking-Water-Hydropac™-Level.pdf
43. https://research.wayne.edu/iacuc/foodwaterrestrictionorregulation
44. https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-technical-document-manganese.html
45. https://animalcare.ubc.ca/sites/default/files/documents/Maintenance of Fluid Homeostasis Dec 2018.pdf
46. https://www.microco.info/cm/349/proposed-maximum-levels-for-the-addition-of-manganese-to-foods-including-food-supplements.pdf
47. https://www.epa.gov/sites/default/files/2014-09/documents/support_cc1_magnese_dwreport_0.pdf

48. https://tera.org/Tools/ratmousevalues.pdf
49. https://www.ncbi.nlm.nih.gov/books/NBK158873/
50. https://www.atsdr.cdc.gov/toxprofiles/tp151-c8.pdf
51. https://nutritionsource.hsph.harvard.edu/manganese/
52. https://iris.epa.gov/static/pdfs/0373_summary.pdf
53. https://www.efsa.europa.eu/en/plain-language-summary/scientific-opinion-tolerable-upper-intake-level-manganese
54. https://semspub.epa.gov/work/03/17141.pdf
55. https://www.atsdr.cdc.gov/toxprofiles/tp151-a.pdf
56. https://www.canada.ca/en/environment-climate-change/services/evaluating-existing-substances/risk-management-scope-manganese-compounds.html
57. https://www.efsa.europa.eu/en/efsajournal/pub/3419
58. https://www.atsdr.cdc.gov/toxguides/toxguide-151.pdf
59. https://www.epa.gov/sites/default/files/2018-12/documents/dw-criteria-manganese.pdf
60. https://www.atsdr.cdc.gov/toxprofiles/tp151.pdf
61. https://www.atsdr.cdc.gov/toxprofiles/tp151-c2.pdf
62. https://www.atsdr.cdc.gov/mrls/pdfs/ATSDR-MRLs-May-2025-H.pdf
63. https://www.ncbi.nlm.nih.gov/books/NBK158864/bin/MRL1.pdf
64. https://pmc.ncbi.nlm.nih.gov/articles/PMC12291727/
65. https://www.ncbi.nlm.nih.gov/gtr/genes/6648/
66. https://www.genecards.org/cgi-bin/carddisp.pl?gene=SOD2
67. https://pmc.ncbi.nlm.nih.gov/articles/PMC2722865/
68. https://www.science.gov/topicpages/s/sod2+gene+polymorphisms.html
69. https://aacrjournals.org/cebp/article/17/12/3298/67048/Target-Sequence-Polymorphism-of-Human-Manganese
70. https://www.science.org/doi/10.1126/sageke.2001.1.tg12
71. https://pmc.ncbi.nlm.nih.gov/articles/PMC193565/
72. https://www.pnas.org/doi/10.1073/pnas.1632471100
73. https://www.uniprot.org/uniprotkb/F5GXZ9/entry
74. https://pubmed.ncbi.nlm.nih.gov/27212182/
75. https://en.wikipedia.org/wiki/SOD2
76. https://www.sciencedirect.com/science/article/pii/S0021925820614387
77. https://www.sciencedirect.com/science/article/pii/S2451945618300072
78. https://www.mygenefood.com/genes/longevity-genes/sod2/
79. https://pmc.ncbi.nlm.nih.gov/articles/PMC12291727/
80. https://www.ncbi.nlm.nih.gov/gtr/genes/6648/

81. https://pmc.ncbi.nlm.nih.gov/articles/PMC193565/
82. https://www.pnas.org/doi/10.1073/pnas.1632471100
83. https://pubmed.ncbi.nlm.nih.gov/27212182/
84. https://onlinelibrary.wiley.com/doi/10.1002/cbf.1761
85. https://diabetesjournals.org/diabetes/article/56/1/265/12838/A-Functional-Polymorphism-in-the-Manganese
86. https://pmc.ncbi.nlm.nih.gov/articles/PMC6139213/
87. https://aacrjournals.org/cebp/article/17/12/3298/67048/Target-Sequence-Polymorphism-of-Human-Manganese
88. https://www.sciencedirect.com/science/article/abs/pii/S0013935123004176
89. https://www.atsdr.cdc.gov/toxprofiles/tp151-c8.pdf
90. https://www.efsa.europa.eu/en/plain-language-summary/scientific-opinion-tolerable-upper-intake-level-manganese
91. https://pmc.ncbi.nlm.nih.gov/articles/PMC5687767/
92. https://nutritionsource.hsph.harvard.edu/manganese/
93. https://www.efsa.europa.eu/en/efsajournal/pub/3419
94. https://www.semanticscholar.org/paper/The-kinetics-of-the-effect-of-manganese-on-SOD2-in-Ghneim/c7c5e1ca8d0b391ab327a15370fc0c515066f4fc
95. https://www.sciencedirect.com/science/article/pii/S0021925820657490
96. https://pmc.ncbi.nlm.nih.gov/articles/PMC3418666/
97. https://pmc.ncbi.nlm.nih.gov/articles/PMC3980854/
98. https://en.wikipedia.org/wiki/SOD2
99. https://pmc.ncbi.nlm.nih.gov/articles/PMC3594688/
100. https://academic.oup.com/biomedgerontology/article/60/4/432/535125
101. https://pubmed.ncbi.nlm.nih.gov/27212182/
102. https://pmc.ncbi.nlm.nih.gov/articles/PMC193565/
103. https://www.pnas.org/doi/10.1073/pnas.1632471100
104. https://pmc.ncbi.nlm.nih.gov/articles/PMC5216654/
105. https://nutritionsource.hsph.harvard.edu/manganese/
106. https://rcastoragev2.blob.core.windows.net/a2026f23a43d9c85e4de018d2bb39678/EFS2-21-e8413.PMC10704406.pdf
107. https://www.nationalacademies.org/read/10026/chapter/12
108. https://www.efsa.europa.eu/en/plain-language-summary/scientific-opinion-tolerable-upper-intake-level-manganese
109. https://www.atsdr.cdc.gov/toxprofiles/tp151-c8.pdf
110. https://www.sciencedirect.com/science/article/abs/pii/S0013935123004176
111. https://www.sciencedirect.com/science/article/pii/S0021925820614387
112. https://pmc.ncbi.nlm.nih.gov/articles/PMC2384167/

113. https://aacrjournals.org/cancerres/article/66/8_Supplement/828/529899/Manganese-superoxide-dismutase-Sod2-enhances
114. https://www.mygenefood.com/genes/longevity-genes/sod2/
115. https://aacrjournals.org/cancerres/article/67/21/10260/533776/Manganese-Superoxide-Dismutase-Enhances-the
116. https://www.semanticscholar.org/paper/The-kinetics-of-the-effect-of-manganese-on-SOD2-in-Ghneim/c7c5e1ca8d0b391ab327a15370fc0c515066f4fc
117. https://pmc.ncbi.nlm.nih.gov/articles/PMC12291727/