Oxidative Stress

as a mechanism for
carcinogenicity of glyphosate

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Antecedents

IARC (2015, p. 399):

- *"There is strong evidence that glyphosate … can act to induce oxidative stress based on studies in experimental animals, and in studies in humans in vitro."*

RAR (2015), Addendum 1, p. iv:

- „… *uncoupling of oxidative phosphorylation by glyphosate has been reported in rat liver microsomes."*

- *"However, **from the sole observation of oxidative stress** and the existence of a plausible mechanism for induction of oxidative stress … **carcinogenic activity … cannot be deduced for glyphosate"***

➔ The „sole observation" should be part of weight of evidence

Kidney tumours in mice – re-cap:

Significant increases in male mice (trend-test, 2-sided)

Year	Strain	Duration (months)	Support by HCD	Dose-dependent
2001	Swiss	18	YES (?)	YES (?)
1997	Crj:CD-1	18	YES	NO
1983	Crl:CD-1	24	No data in RAR but by EPA	YES

Gao et al. (2019): Study in **male** ICR **mice**

- Glyphosate (Sigma, 96% purity,)
- oral (gavage) administration – 28 days
- Significant ↓ of Superoxide dismutase (SOD) and Catalase **in kidneys**
- Significant ↑ of Malondialdehyde (MAD)

Hypothesis:

N-(phosphonomethyl) **glycine** (glyphosate) stimulates ROS-formation via NMDA receptor (glycine is a known agonist)

Proof:

Glyphosate + NMDA receptor-blocker: ↓ in oxidative stress

Glyphosate an „inert“ compound?

- Uncoupling of oxidative phosphorylation in isolated rat liver mitochondria

  (Bababunmi et al. 1979 – referred to in RAR 2015)

- Oxidative stress in kidneys of mice in vivo via NMDA-receptor (glycine)

  (Gao et al. 2019)

- Oxidative stress in testes of rats via gut microbial dysbiosis and subsequent IL-17A/TNF-α signalling

  (Liu et al. 2022)