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SUPPLEMENTARY DATA

Food Microbiology, Safety and Toxicology Public Health Nutrition Policy & Economics

Neurotoxic and neuromotor implications of cyanate, an oxidative byproduct of cyanide derived from linamarin in cassava: A systematic review

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Supplementary File

Newcastle-Ottawa scale for non-randomized studies

From Wells GA, Shea B, O'Connell D, Peterson J, et al. (2021). The Newcastle-Ottawa scale (NOS) for assessing quality of non-randomised studies in meta-analyses. The Ottawa Hospital Research Institute.

Answers: Input the letter (a, b, c, d) based on your quality assessment.
Asterisk ("*") counts as a point towards good quality, below which there is no score.

Reference 1: Rwatambuga FA, Ali ER, Bramble MS, Gosschalk JE, Kim M, Yandju DL, et al. (2020). Motor control and cognition deficits associated with protein carbamoylation in food (cassava) cyanogenic poisoning: Neurodegeneration and genomic perspectives. Food Chem Toxicol, 148: 1-7.

Domain	RVM	ALO	Consensus
1. **Selection – Representatives of Cases** a. Truly representative of the average patient with disease (eg. severity, comorbidities) in the community* b. Somewhat representative of the average (eg severity, comorbidities) * c. Selected group d. No description of the derivation of the cohort/case	b	a	b
2. **Selection – Selection of controls** a. Drawn from the same community as the exposed cohort * b. Drawn from a different source c. No description of the derivation of the non-exposed cohort	a	a	a
3. **Selection – Ascertainment of exposure** a. Secure record (eg surgical or intake records) * b. Structured interview * c. Written self-report d. No description	a	d	a
4. **Selection – Demonstration that outcome of interest was not present at the start of the study** a. Yes * b. No	b	b	b
5. **Comparability – Comparability of cohorts/cases on the basis of design or analysis** a. Study controls for age, ethnicity, gender* (age) b. Study controls for any additional factor * c. Inadequate degree of control	a	a	a
6. **Outcome – Assessment of outcome** a. Independent blind assessment * b. Record linkage * c. Self-report d. No description	a	a	a
7. **Outcome – Was follow-up long enough for outcomes to occur?** a. Yes *	a	a	a

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b. No			
8. **Outcome – Adequacy of follow-up** a. Complete follow-up, all subjects accounted for * b. Subjects lost to follow-up unlikely to introduce bias – small number lost (<20%) * c. Follow-up rate > 20% and no description of lost to follow-up. d. No statement	a	a	a

Summary: (*low quality, **medium quality, ***high-quality*)

1. **Selection:** ***high-quality
2. **Comparability:** ***high-quality
3. **Outcome:** ***high-quality

Supplementary File

SYRCLE risk-of-bias tool

From Hoojimans CR, Rovers MM, de Vries RBM, et al. (2014). SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol, 14:43.

Answers: Yes, No, or Unclear (*not mentioned in the article*)

Reference 1: Tor-Agbidye J, Palmer VS, Spencer PS, Craig AM, Blythe LL, Sabri MI. (1999). Sodium cyanate alters glutathione homeostasis in rodent brain: relationship to neurodegenerative diseases in protein-deficient malnourished populations in Africa. Brain Res, 820(1-2): 12-19.

Domain	RVM	PJR	ALO	Consensus
1. **Selection bias** – Was the allocation sequence adequately generated and applied?			Unclear	
2. **Selection bias** – Were the groups similar at baseline or were they adjusted for confounders in the analysis?			Yes	
3. **Selection bias** – Was the allocation adequately concealed?			Unclear	
4. **Performance bias** - Were the animals randomly housed during the experiment? (*for cell lines:* Were cells inoculated randomly in wells prior to exposure assignment during the experiment?)			No	
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7. **Detection bias** – Was the outcome assessor blinded?			Unclear	
8. **Attrition bias** – Were incomplete outcome data adequately addressed?			Yes	
9. **Reporting bias** – Are reports of the study free of selective outcome reporting?			Yes	
10. **Others** – Was the study apparently free of other problems that could result in high risk of bias?			Yes	

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Reference 2: Huang C-W, Huang C-C, Huang M-H, Wu S-N, Hsieh Y-J. (2005). Sodium cyanate-induced opening of calcium-activated potassium currents in hippocampal neuron-derived H19-7 cells. Neurosci Lett, 337: 110-114.				
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Reference 3: Tellez I, Johnson D, Nagel RL, Cerami A. (1979). Neurotoxicity of sodium cyanate: New pathological and ultrastructural observations in *Maccaca nemestrina*. Acta Neuropathol, 47: 75-79.

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Reference 4: Kimani S, Sinei K, Bukachi F, Tshala-Katumbay D, Maitai C. (2014). Memory deficits associated with sublethal cyanide toxicity in rodents. Metab Brain Dis, 29(1): 105-112.				
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Reference 5: Kassa RM, Kasensa NL, Monterroso VH, Kayton RJ, Klimek JE, et al. (2011). On the biomarkers of konzo, a distinct upper motor neuron disease associated with food (cassava) cyanogenic exposure. Food Chem Toxicol, 49(3): 571-578.

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Reference 6: Kimani S, Monterroso VH, Lasarev M, Kipruto S, Bukachi F, et al. (2013). Carbamoylation correlates of cyanate neuropathy and cyanide poisoning: relevance to the biomarkers of cassava cyanogenesis and motor system toxicity. SpringerPlus, 2: 647.

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Reference 7: Kimani S, Moterroso V, Morales P, Wagner J, Kipruto S, et al. (2014). Cross-species and tissue variations in cyanide detoxification rates in rodents and non-human primates on protein-restricted diet. Food Chem Toxicol, 66: 203-209.				
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Reference 8: Choi H-J, Lee S-H. (2017). Cyanate induces Apoptosis of Rat Glioma Cell Line. J Life Sci, 27(3): 267-264.				
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Reference 10: Alter BP, Kan YW, Nathan DG. (1974). Toxic effects of High-Dose Cyanate Administration in Rodents. Blood, 43(1): 69-77.				
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