

The Correspondence section is not peer-reviewed. Personal opinions expressed herein are the sole responsibility of the authors. EHP neither endorses nor disputes the content of the letters it publishes.

Comment on "Rheumatoid Arthritis in Agricultural Health Study Spouses: Associations with Pesticides and Other Farm Exposures"

<http://dx.doi.org/10.1289/EHP730>

Refers to <http://dx.doi.org/10.1289/EHP129>

We read the paper by Parks et al. with interest, particularly the increased risk of rheumatoid arthritis (RA) reported for maneb and mancozeb pesticide use (odds ratio [OR] = 3.3; 95% confidence interval [CI]: 1.5, 7.1). We suggest that these findings are explained by heavy metal exposure.

Maneb and mancozeb fungicides are approximately 21% manganese by weight (Gunier et al. 2014). Their use is associated with increasing concentrations of manganese in house dust from Californian farm worker residences, and manganese concentrations decline with distance from use (Gunier et al. 2014). Mancozeb use results in raised local sediment concentrations of manganese, as demonstrated by long-term use in banana plantations (Melgar et al. 2008).

Other farm exposures may predispose individuals to metals inhalation. The authors report an association between RA and chemical fertilizer application (OR = 1.7; 95% CI: 1.1, 2.7). Phosphate fertilizers can contain cadmium as a contaminant in phosphate rock, with rates of cadmium contamination in soil ranging from 0.3 to 1.2 g/ha (Mortvedt 1987).

Of note, this group has previously demonstrated welding to be associated with RA in women (OR = 2.1; 95% CI: 0.8, 5.4) (De Roos et al. 2005), as welding fumes are associated with inhalation of both cadmium and manganese particles.

Furthermore, in the current study Parks et al. demonstrated increased RA risk

with >18 pack years smoking (OR = 1.5; 95% CI: 1.0, 2.2). Cadmium is among the hazardous components of cigarette smoke, and the mean whole blood cadmium concentration in smokers has been reported as double that of nonsmokers ($2.67 \pm 1.21 \mu\text{g/L}$ versus $1.37 \pm 0.45 \mu\text{g/L}$) (Bernhard et al. 2005).

We propose that inhalation of soil dust contaminated with manganese and cadmium may be a cause of RA. Cadmium exposure has been hypothesized as a trigger for RA, providing a common thread between smoking and many other known RA risk factors (Hutchinson 2015). This hypothesis is supported by a rat model that exhibited enhanced collagen-induced arthritis disease activity when exposed to high levels of cadmium (Ansari et al. 2015).

Inhalation exposure is relevant as the lung is an important initiating site of seropositive RA, due to local generation of anti-citrullinated peptide antibody (Perry et al. 2014). Cadmium and manganese have the potential to cause citrullination within the lung as calcium channel activators, significantly raising intracellular calcium levels (Hinkle et al. 1992).

Future studies investigating the link between RA, pesticides, and other farm exposures should consider exposures to metals as potential risk factors.

Support for the authors is provided by Cornwall Arthritis Trust. The authors declare they have no actual or potential competing financial interests.

Daniel Murphy,^{1,2} James Pay,² Rebecca Benham,² Benjamin James,² and David Hutchinson^{1,2}

¹Rheumatology Department, Royal Cornwall Hospital, Truro, Cornwall, United Kingdom; ²University of Exeter Medical School, Truro, Cornwall, United Kingdom

Address correspondence to D. Murphy, Rheumatology Department, Royal Cornwall Hospital, Truro, Cornwall, TR1 3LJ United Kingdom. E-mail: daniel.murphy8@nhs.net

Note to readers with disabilities: EHP strives to ensure that all journal content is accessible to all readers. However, some figures and Supplemental Material published in EHP articles may not conform to 508 standards due to the complexity of the information being presented. If you need assistance accessing journal content, please contact ehponline@niehs.nih.gov. Our staff will work with you to assess and meet your accessibility needs within 3 working days.

REFERENCES

- Ansari MM, Neha, Khan HA. 2015. Effect of cadmium chloride exposure during the induction of collagen induced arthritis. *Chem Biol Interact* 238:55–65, doi:10.1016/j.cbi.2015.06.001.
- Bernhard D, Rossmann A, Wick G. 2005. Metals in cigarette smoke. *IUBMB Life* 57(12):805–809, doi:10.1080/15216540500459667.
- De Roos AJ, Cooper GS, Alavanja MC, Sandler DP. 2005. Rheumatoid arthritis among women in the Agricultural Health Study: risk associated with farming activities and exposures. *Ann Epidemiol* 15(10):762–770, doi:10.1016/j.annepidem.2005.08.001.
- Gunier RB, Jerrett M, Smith DR, Jursa T, Yousefi P, Camacho J, et al. 2014. Determinants of manganese levels in house dust samples from the CHAMACOS cohort. *Sci Total Environ* 497:360–368, doi:10.1016/j.scitotenv.2014.08.005.
- Hinkle PM, Shanshala ED, Nelson EJ. 1992. Measurement of intracellular cadmium with fluorescent dyes. Further evidence for the role of calcium channels in cadmium uptake. *J Biol Chem* 267(35):25553–25559, PMID:1281160.
- Hutchinson D. 2015. Cadmium, one of the villains behind the curtain: has exposure to cadmium helped to pull the strings of seropositive rheumatoid arthritis pathogenesis all along? *Int J Rheum Dis* 18:570–573, doi:10.1111/1756-185X.12673.
- Melgar C, Geissen V, Cram S, Sokolov M, Bastidas P, Ruiz Suárez LE, et al. 2008. Pollutants in drainage channels following long-term application of mancozeb to banana plantations in southeastern Mexico. *J Soil Sci Plant Nutr* 171(4):597–604, doi:10.1002/jpln.200700171.
- Mortvedt JJ. 1987. Cadmium levels in soils and plants from some long-term soil fertility experiments in the United States of America. *J Environ Qual* 16(2):137–142, doi:10.2134/jeq1987.00472425001600020008x.
- Perry E, Kelly C, Eggleton P, De Soyza A, Hutchinson D. 2014. The lung in ACPA-positive rheumatoid arthritis: an initiating site of injury? *Rheumatology* (Oxford) 53(11):1940–1950, doi:10.1093/rheumatology/keu195.