

Avis du Conseil scientifique Sclérose systémique Exposition aux solvants et au formaldéhyde

19-10-2023

Sclérose systémique liée à l'exposition aux solvants et au formaldéhyde

Résumé de l'avis du Conseil scientifique de Fedris du 19 octobre 2023

Le Conseil scientifique, sur base de l'avis de la Commission médicale « agents chimiques et toxiques » constate qu'il n'existe actuellement pas suffisamment de preuves scientifiques d'un risque accru de développer une sclérose systémique chez les travailleurs exposés aux solvants et par conséquent, d'éléments permettant de démontrer l'existence d'un lien causal prépondérant. Il n'est pas non plus possible d'identifier les solvants concernés et de définir des critères d'exposition. Les conditions nécessaires pour inscrire la sclérose systémique provoquée par l'exposition aux solvants et au formaldéhyde dans le système liste des maladies professionnelles ne sont donc pas rencontrées.

La sclérose systémique est une maladie rare du tissu conjonctif caractérisée par une hyperactivité et un remodelage vasculaire, une activation des fibroblastes et une synthèse de la matrice-extracellulaire. La prévalence de cette maladie a été estimée entre 7,2 et 33,9 pour 100 000 individus en Europe.

En 2023, le Prof. T Nawrot a réalisé une étude de la littérature épidémiologique de ces 20 dernières années (2001-2022) : « Solvent and formaldehyde exposure and systemic sclerosis, a systematic overview of the current evidence ».

Sur base de cette étude, la Commission médicale « agents chimiques et toxiques » a constaté que, dans l'ensemble, les études scientifiques montrent des associations significatives entre la sclérose systémique et l'expositions aux solvants. Cependant, il est impossible d'attribuer cette association à des solvants spécifiques ou d'établir des relations doses/réponses. En effet, dans la majorité des études analysées, l'exposition est basée sur la description du poste de travail, le titre du poste ou les expositions déclarées par le biais d'un questionnaire ; l'information détaillée sur la durée et l'intensité de l'exposition ou le solvent incriminé manque.

La commission conclut qu'il n'y a pas encore, à ce jour, assez d'éléments dans littérature pour démontrer un lien de causalité clair, établir un seuil de doublement du risque et fixer des critères d'exposition pour les différents solvants organiques et/ou le formaldéhyde.

Le Conseil scientifique a approuvé l'étude réalisée par le Prof. Nawrot et les conclusions de la commission « agents chimiques et toxiques »

Références

- Cutolo M and Smith V. Nailfold capillaroscopy and other methods to assess the microvasculopathy in SSc. In: Hachulla E et al, eds. EULAR Textbook on Systemic Sclerosis, 2013.
- Smith V and De Keyser F. Advances in therapies for systemic sclerosis. In: Clinical Therapy Research in the Inflammatory Diseases, edited by Van Vollenhoven R. Singapore: World Scientific Publishing Co. Pte. Ltd, 2015, p. 165-198.
- van den Hoogen et al. 2013 classification criteria for SSc: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis.2013
- LeRoy and Medsger. Criteria for the classification of early SSc. J Rheumatol.2001.
- Vanthuyne M, Smith V, De Langhe E, Van Praet J, Arat S, Depresseux G, Westhovens R, Blockmans D, Badot V, Cogan E, De Keyser F, Houssiau FA. The Belgian Systemic Sclerosis Cohort: Correlations between Disease Severity Scores, Cutaneous Subsets and Autoantibody Profile. J Rheumatol.2012.
- Erasmus, L.D. Scleroderma in goldminers on the Witwatersrand with particular reference to pulmonary manifestations S Afr Lab Clin Med (1957) 3:209-231
- Diot, E., Lesire, V., Guilmot, J.L., Metzger, M.D., Pilore, R., Rogier, S., Stadler, M., Diot, P., Lemarie, E. and Lasfargues, G. Systemic sclerosis and occupational risk factors: a case-control study Occup Environ Med (2002) 59:545-549
- Smith, V., Vanthuyne, M., Vander Cruyssen, B., Van Praet, J., Vermeiren, F., Smets, H., Houssiau, F. and De Keyser, F. Over-representation of construction-related occupations in male patients with systemic sclerosis Ann Rheum Dis (2008) 67: 1448-1450
- Marie, I., Gehanno, J.F., Bubenheim, M., Duval-Modeste, A.B., Joly, P., Dominique, S., Bravard, P., Noël, D., Cailleux, A.F., Weber, J., Lagoutte, P., Benichou, J. and Levesque, H. Prospective study to evaluate the association between systemic sclerosis and occupational exposure and review of the literature Autoimmunity Reviews (2014) 13:151-156
- De Decker, E.v, Vanthuyne, M., Blockmans, D., Houssiau, F., Lenaerts, J., Westhovens, R., Nemery, B. and De Langhe, E. High prevalence of occupational exposure to solvents or silica in male systemic sclerosis patients: a Belgian cohort analysis Clin Rheumatol (2018) 37:1977-1982
- McCormic, Z.D., Khuder, S.S., Aryal, B.K., Ames, A.L. and Khuder, S.A. Occupational silica exposure as a risk factor for scleroderma: a meta-analysis Int Arch Occup Environ Health (2010) 83:763-769
- Note des rédacteurs : L'étude suivante dont les résultats ont été rendus publiques en 2023 n'a pas été intégrée à l'étude, mais elle a été présentée en séance au Conseil scientifique qui a donc pu l'analyser avant de rendre son avis : Muntyanu A., Milan R., Rahme E., Baron M., Netchiporuk E. Organic solvent exposure and systemic sclerosis: A retrospective cohort study based on the Canadian Scleroderma Research Group registry. J Am Acad Dermatol. 2024 Mar;90(3):605-607. doi: 10.1016/j.jaad.2023.04.062. Epub 2023 May 13.
- Rubio-Rivas, M., Moreno, R. and Corbella, X. Occupational and environmental scleroderma. Systematic review and meta-analysis Clin Rheumatol (2017) 36:569-582
- Beer, C., Schlünssen, V., Sherson, D., Troldborg, A., Nielsen, B.D., Olesen, A.B., Jacobsen, G., Sondergaard, K. and Kolstad H.A. Exposure to quartz dust/sand (crystalline silica) and the risk of development of connective tissue diseases (for instance scleroderma) and kidney diseases (for instance glomerulonephritis) (April 2 nd 2015) <https://www.aes.dk/~media/ASK/pdf/Eudvalget/Exposure%20to%20quartz%20dust%20or%20sand%20and%20the%20risk%20of%20development%20of%20connective%20tissue%20diseases.pdf.ashx>
- Bradshaw, L., Bowen, J., Fishwick, D. and Powell, S. Health surveillance in silica exposed workers HSE RR827 Healt Report 2010 <http://www.hse.gov.uk/research/rrpdf/rr827.pdf>

Solvent and formaldehyde exposure and systemic sclerosis, a systematic overview of the current evidence

Summary

Systemic sclerosis is a rare autoimmune disease with a multifactorial etiology. This document provides a systematic overview of the epidemiological evidence during the last 20 years, between systemic sclerosis and the possible occupational aetiologies due to solvent exposure.

In total we retrieved 10 studies of which 1 cohort, 7 case-controls and 2 descriptive studies of exposure prevalence in diseased populations. Seven of the eight analytical studies (1 cohort and 7 case-control studies) published in the last 20 years showed significant associations, with ORs ranging from 1.03 to 3.2. The most recent meta-analysis was published in 2016 and included 13 case-control studies and comprised 2107 patients. The combined Odds was OR 2.00 (95% CI 1.32–3.02; $p = 0.001$). Based on the reported literature and assuming a causal relationship we can estimate that in patients with SSc and proven occupational exposure to solvents, 65% to 50% (Attributable fraction of exposed) of SSc could be attributed to occupational exposure to solvents. However, to date the literature is not specific enough to establish dose-response relationships for different organic solvents and or formaldehyde as the majority of studies exposure is based on job description, job title or self-reported exposures via questionnaire, but not on actual dose-response associations in which exposure took into account the duration or intensity (with exception of 1 study for styrene).

Overall, there is consistency in the literature regarding the association between solvent exposure and scleroderma. However, is impossible to address this to specific solvents nor to provide a threshold for a doubling of the risk. While there is some consistency in the literature, the lack of comprehensive knowledge and a clear dose-response relationship limits our ability to establish causality.

References

1. Dumoitier N, Lofek S, Mounthon L. Pathophysiology of systemic sclerosis: state of the art in 2014. *Presse Med* 2014; **43**(10 Pt 2): e267-78.
2. Bergamasco A, Hartmann N, Wallace L, Verpillat P. Epidemiology of systemic sclerosis and systemic sclerosis-associated interstitial lung disease. *Clin Epidemiol* 2019; **11**: 257-73.
3. Thoreau B, Chaigne B, Renaud A, Mounthon L. Pathophysiology of systemic sclerosis. *Presse Med* 2021; **50**(1): 104087.
4. Aryal BK, Khuder SA, Schaub EA. Meta-analysis of systemic sclerosis and exposure to solvents. *Am J Ind Med* 2001; **40**(3): 271-4.
5. Critical Appraisal Skills Programme. CASP Case-Control Checklist. 2022. <https://casp-uk.net/casp-tools-checklists/> (accessed May 12th 2022).
6. Garabrant DH, Lacey JV, Jr., Laing TJ, et al. Scleroderma and solvent exposure among women. *Am J Epidemiol* 2003; **157**(6): 493-500.
7. Hjuler Boudigaard S, Stokholm ZA, Vestergaard JM, et al. A follow-up study of occupational styrene exposure and risk of autoimmune rheumatic diseases. *Occup Environ Med* 2020; **77**(2): 64-9. Czirák L, Kumánovics G. Exposure to solvents in female patients with scleroderma. *Clin Rheumatol* 2002; **21**(2): 114-8.
8. De Decker E, Vanthuyne M, Blockmans D, et al. High prevalence of occupational exposure to solvents or silica in male systemic sclerosis patients: a Belgian cohort analysis. *Clinical Rheumatology* 2018; **37**(7): 1977-82.
9. Diot E, Lesire V, Guilmot JL, et al. Systemic sclerosis and occupational risk factors: a case-control study. *Occup Environ Med* 2002; **59**(8): 545-9.
10. Bovenzi M, Barbone F, Pisa FE, et al. A case-control study of occupational exposures and systemic sclerosis. *Int Arch Occup Environ Health* 2004; **77**(1): 10-6.
11. Maître A, Hours M, Bonneterre V, et al. Systemic sclerosis and occupational risk factors: role of solvents and cleaning products. *J Rheumatol* 2004; **31**(12): 2395-401.
12. Marie I, Gehanno JF, Bubenheim M, et al. Prospective study to evaluate the association between systemic sclerosis and occupational exposure and review of the literature. *Autoimmun Rev* 2014; **13**(2): 151-6.
13. Kutting B, Uter W, Drexler H. Is occupational exposure to solvents associated with an increased risk for developing systemic scleroderma? *J Occup Med Toxicol* 2006; **1**: 15.
14. Bobeica C, Niculeț E, Craescu M, et al. Etiological factors of systemic sclerosis in the southeast region of Romania. *Exp Ther Med* 2021; **21**(1): 79.
15. Kettaneh A, Al Moufti O, Tiev KP, et al. Occupational exposure to solvents and gender-related risk of systemic sclerosis: a metaanalysis of case-control studies. *J Rheumatol* 2007; **34**(1): 97-103.
16. Barragan-Martinez C, Speck-Hernandez CA, Montoya-Ortiz G, Mantilla RD, Anaya JM, Rojas- Villarraga A. Organic solvents as risk factor for autoimmune diseases: a systematic review and meta-analysis. *PLoS One* 2012; **7**(12): e51506.
17. Rubio-Rivas M, Moreno R, Corbella X. Occupational and environmental scleroderma. Systematic review and meta-analysis. *Clin Rheumatol* 2017; **36**(3): 569-82.
18. Imbriani M, Ghittori S. Gases and organic solvents in urine as biomarkers of occupational exposure: a review. *Int Arch Occup Environ Health* 2005; **78**(1): 1-19.
19. Piantoni S, Franceschini F, Fredi M, Andreoli L, Tincani A. Chapter 29 - Topoisomerase I (SCL 70) Autoantibodies. In: Shoenfeld Y, Meroni PL, Gershwin ME, eds. Autoantibodies (Third Edition). San Diego: Elsevier; 2014: 239-45.
20. Ban M, Langonne I, Huguet N, Pepin E, Morel G. Inhaled chemicals may enhance allergic airway inflammation in ovalbumin-sensitised mice. *Toxicology* 2006; **226**(2-3): 161-71.
21. Iavicoli I, Marinaccio A, Carelli G. Effects of occupational trichloroethylene exposure on cytokine levels in workers. *J Occup Environ Med* 2005; **47**(5): 453-7.
22. Jia X, Jia Q, Zhang Z, et al. Effects of formaldehyde on lymphocyte subsets and cytokines in the peripheral blood of exposed workers. *PLoS One* 2014; **9**(8): e104069.

23. Nietert PJ, Sutherland SE, Silver RM, Pandey JP, Dosemeci M. Solvent oriented hobbies and the risk of systemic sclerosis. *J Rheumatol* 1999; **26**(11): 2369-72.
24. Nietert PJ, Sutherland SE, Silver RM, et al. Is occupational organic solvent exposure a risk factor for scleroderma? *Arthritis & Rheumatism* 1998; **41**(6): 1111-8.
25. Purdue M, Zhang L, Vermeulen R, et al. Occupational trichloroethylene exposure and antinuclear antibodies: a cross-sectional study in China. *Occupational and Environmental Medicine* 2022; **79**(10): 717.
26. Stochmal A, Czuwara J, Trojanowska M, Rudnicka L. Antinuclear Antibodies in Systemic Sclerosis: an Update. *Clinical Reviews in Allergy & Immunology* 2020; **58**(1): 40-51.