Indoor mould exposure, asthma and rhinitis: findings from systematic reviews and recent longitudinal studies

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Methods

The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) commissioned an assessment by a working group of 13 experts with complementary areas of expertise (epidemiologists, clinicians, toxicologists, microbiologists, mycologists, sociologists, health geographers, socio-economists and building engineers), who convened over 10 days in 2014-2016: 1) To make a state of art of health effect due to exposure to mould in indoor environment, 2) To make a state of art of environmental methods (air, dust, materials), 3) To characterize population groups at risk, and 4) to identify factors of building involved in the development of mould.

Concerning the health effect due to exposure to mould in indoor environment, human and animal data were taken into account to assess the recent findings. An analysis of dose-response relationship was achieved in order to define a health threshold corresponding to a level of concentration below which no effect on health is expected for the general population. Toxicological data dealing mainly with potential mechanisms behind the observed health effect, and animal studies were considered in interpreting the evidence of health effect due to mould exposure.

A full report was published in French in August 2016 (Moisissures dans le bâti. Avis et rapport d’expertise collective. Agence nationale de sécurité sanitaire - alimentation, environnement et travail. French Agency for Food, Environmental and Occupational Health & Safety, . Maisons-Alfort 2016. p. 1-344) and a short ANSES’ opinion is available in English (Revised opinion of the French Agency for Food, Environmental and Occupational Health and Safety on Mould in buildings: www.anses.fr/en/system/files/AIR2014SA0016EN.pdf. 2016).
Legends for figures

Figure E1: Literature search based on the four-phase flow diagram of PRISMA statement.
Table E1. Exposure to moulds using quantitative measurements and asthma occurrence in children – longitudinal studies.

| References | Study design | Mould exposure | Main outcomes | Results |
|------------|--------------|----------------|---------------|---------|
| Douwes Netherlands (112) | Birth cohort n=690 | Main living quarter floor dust Extracellular Polysaccharides EPS (Penicillium/ Aspergillus) Glucans | Doctor-diagnosed (DD) asthma Parents’ ISAAC Questionnaire at 1, 2, 3, 4 years. | EPS DD Asthma aOR [95 CI] |
| | | | | 1<Children<7 years Incident wheezing |
| Iossifova USA (113) | Birth cohort CCAPS n=574 | Main living quarter floor dust glucans at 8 months | Recurrent wheeze (13 months) | EP2 DD Asthma aOR [95 CI] |
| | | | Glucans low vs high: quartile 1 vs 4 Q1 <22 µg/g aOR 3.04 [1.25-7.38] Q4 >120 µg/g aOR 0.39 [0.16-0.93] |
| Iossifova USA (114) | Birth cohort CCAPS n=483 | Idem | Asthma predictive index (3 years) | EP2 DD Asthma aOR [95 CI] |
| | | | Glucans NS Q1 aOR 3.4 [0.5-23.5] Q4 aOR 0.6 [0.2-1.6] |
| Dales Canada (101) | Birth cohort n=357 | Airborne ergosterol and glucans within first year of life | Respiratory illness from birth to 2 years | Glucans, ergosterol NS |
| Rosenbaum USA (29) | Birth cohort n=103 | LR airborne moulds at 3 months | Wheeze (1 year) | Penicillium high >120 CFU/m3 vs ND aOR 6.18 [1.3-28.5] |
| Tischer Germany Netherlands (115) | (678) Nested Case Control | LR floor and bedroom mattress dust EPS Glucans | DD asthma (6 years) | EP2 per interquartile range DD Asthma OR 0.60 [0.39-0.92] |
| Reponen USA (19) | Birth cohort CCAPS n=176 | Idem Iossifova + Environmental Relative Mouldiness Index (ERMI) | Asthma (7 years) | EP2 Asthma aOR [95 CI] |
| Reponen USA : (116) | Birth cohort CCAPS n=289 | Idem | 10 unit rise ERMI value aRR: 1.8 [1.5-2.2] |
| Behbod 2013 USA (27) | Birth cohort n=499 | Bedroom floor dust at 3 months Interquartile increase in mould concentration | Any Wheeze (≥1vs 0 episode) First year of life | Alternaria: OR 1.83 [1.07-3.14] Cladosporium : OR=1.47 [1.16-1.85] Yeasts: OR 0.78 [0.66-0.93] |
| Dannemiller USA (30) | Nested Case Control | Main living quarter floor dust Next generation sequencing. qPCR. | Asthma (7 years) | Low diversity OR 4.80 [1.04-22.1] qPCR : NS |
| Behbod 2015 USA (28) | Birth cohort n=408 | Idem Behbod 2013+ indoor airborne moulds (CFU/m³) | Current asthma (13 years) | Dust yeasts HR=0.86 [0.75-0.98] Airborne Alternaria Q4 ≥ 11.1 vs <11.1 CFU/m³:HR 1.70 [1.01-2.86] |
| Tisher 2016 USA (31) | Lisa birth cohort 189 homes | LR floor dust at 3 months Bacterial and fungal diversity (terminal restriction fragment length polymorphisms | Sensitization at 6 and 10 yrs Current wheeze at 10 years | Adjusted logistic regression Higher fungal diversity associated to: Sensitization at 6: aOR=0.26 [0.1-0.7] -Wheeze at 10: aOR=0.42 [0.18-0.96] Longitudinal analyses (GEE): NS |
| Shorter NewZeland (22) | Nested Incident Cases n=150 Controls n=300 | Beddrom wall (electrostatic dust cloth) for 4 weeks qPCR moulds | 1<Children<7 years Incident wheezing | No relationship with qPCR |

CCAPS: Cincinnati Childhood Allergy and Pollution Study; C: Control; DD: Doctor-Diagnosed; EPS: Extracellular PolySaccharides, ERMI: Environmental Relative Moldiness Index; LR: Living Room; ND: not detected; NS: not significant; Q: quartile
Table E2: Exposure to moulds using qualitative metrics and asthma in adults – Longitudinal studies

| References      | Study design                                      | Mould exposure                                                                 | Main outcomes                                                                 | Results                                                                 |
|-----------------|---------------------------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Jaakkola 2006 Finland (36) | Population-based incident case-control study n= 521 new asthma cases / n=932 controls (21-63 years old) | Questionnaire data on visible mould, and mould odour at home and indoors at work | Diagnosed asthma defined as the occurrence of at least one asthma-like symptom and reversible airways obstruction in lung function | Adjusted OR for incident asthma with reference = no mould, no carpet   |
|                 |                                                   |                                                                                |                                                                               | aOR, 95% CI                                                            |
|                 |                                                   |                                                                                |                                                                               |                                                                         |
|                 |                                                   |                                                                                |                                                                               |                          Home environment                     |
|                 |                                                   |                                                                                |                                                                               |                                                                         |
|                 |                                                   |                                                                                |                                                                               |                          Mould, no carpet     1.10 (0.76-1.59)   |
|                 |                                                   |                                                                                |                                                                               |                          Mould + carpet           1.51 (0.30-7.64)   |
|                 |                                                   |                                                                                |                                                                               |                          Work environment                        |
|                 |                                                   |                                                                                |                                                                               |                          Mould, no carpet     1.39 (0.91-2.13)   |
|                 |                                                   |                                                                                |                                                                               |                          Mould + carpet          4.64 (1.11-19.4)   |
| Gunnbjörnsdóttir 2006 Iceland, Norway, Sweden, Denmark, and Estonia (37) | Respiratory Health in Northern Europe (RHINE) study. A population-based cohort of adults aged 20–44 years at baseline and followed up after 7-9 years N= 16 190 | Cross sectional analysis Self-reported water damage or visible mould in the last 12 months. Longitudinal analysis Retrospective self-report of any sign of dampness in the home since the baseline survey. | Prevalence, incidence and remission of respiratory symptoms and asthma | OR for respiratory symptoms in subjects living in damp housing since the baseline survey |
|                 |                                                   |                                                                                |                                                                               |                                                                         |
|                 |                                                   |                                                                                |                                                                               |                          wheeze               1.28 (1.12-1.46)   |
|                 |                                                   |                                                                                |                                                                               |                          nocturnal breathlessness 1.33 (1.09-1.63)   |
|                 |                                                   |                                                                                |                                                                               |                          nocturnal cough        1.26 (1.13-1.41)   |
|                 |                                                   |                                                                                |                                                                               |                          asthma                1.13 (0.92-1.40)   |
|                 |                                                   |                                                                                |                                                                               |                          remission              0.68 (0.48-0.96)   |
|                 |                                                   |                                                                                |                                                                               |                          wheeze               0.88 (0.74-1.03)   |
|                 |                                                   |                                                                                |                                                                               |                          nocturnal breathlessness 0.68 (0.48-0.96)   |
|                 |                                                   |                                                                                |                                                                               |                          nocturnal cough        0.84 (0.73-0.97)   |
|                 |                                                   |                                                                                |                                                                               |                          asthma                0.65 (0.36-1.17)   |
| Norbäck 2011 (38) | Population-based longitudinal study Europe (ECRHS I & II) N = 6443 adults aged 20-45 years at baseline and followed up after 9 years, with lung function measurements | Self-reported questionnaire data on visible mould, water damage, dampness + home visit for 3118 subjects at follow-up. Dampness score and mould score as sum of positive answers at baseline + follow-up. | Longitudinal decline in forced expiratory volume in 1 s (FEV1) | No association between mould exposure (reported or observed) and FEV1 decline  |
|                 |                                                   |                                                                                |                                                                               |                         Association between FEV1 decline and dampness, only in women: additional decline in FEV1 -2.25 ml/year (95% CI -4.25 to -0.25), [-3.00 ml/year (95% CI -5.00 to -0.99) after excluding women with asthma at baseline] Significant trend for FEV1 decline in relation to |
### References

| Study design | Mould exposure | Main outcomes | Results |
|--------------|----------------|---------------|---------|
| Population-based longitudinal study, N = 7104 20-45 year-old adults without asthma or asthma-like symptoms at baseline, and followed up after 9 years | Self-reported questionnaire data on visible mould, water damage, dampness in the last 12 months and “ever” + home at follow-up. Dampness score and mould score as sum of positive answers at baseline + follow-up | Asthma Incidence (also consider onset of asthma+bronchial hyperresponsiveness) | Excess risk of new onset asthma |
| Norbäck 2013 (39) | | | |

| Reported Exposure at baseline | Relative Risk (95%CI) |
|-------------------------------|-----------------------|
| Water damage 12mo             | 1.46 (1.09 to 1.94)   |
| Indoor moulds 12mo            | 1.30 (1.00 to 1.68)   |
| Moulds in bedroom (ever)      | 1.08 (0.79 to 1.48)   |
| Moulds in living room (ever)  | 1.34 (0.91 to 1.97)   |
| Mould score (baseline + follow-up) | | |
| Score 0                       | 1 (ref.)          |
| Score 1–2                     | 1.05 (0.82 - 1.33)  |
| Score 3–4                     | 1.73 (1.27 - 2.37)  | p for trend | 0.007 |
| Observed exposure at follow-up| | |
| Any damp spots                | 1.49 (1.00 to 2.22)  |
| Any visible mould             | 1.15 (0.71 to 1.85)  |

Stronger effect in those with multisensitisation and in those sensitised to moulds.
Table E3. Summary of conclusions of the IOM and WHO, and the findings of the ANSES regarding the association between health outcomes and exposure to indoor moulds

| Health Outcomes | IOM (2004) | WHO (2009) | ANSES (2016) |
|-----------------|------------|------------|--------------|
|                 | Association between health outcomes and the presence of mould or other agents in damp indoor environments | Association between respiratory health outcomes and indoor dampness-related agents | Mould exposure and health outcomes |
|                 | Epidemiological data mainly cross-sectional until 2003 | Epidemiological data mainly from cross-sectional studies published between mid-2003 and 2007 | Epidemiological data mainly from meta-analyses, systematic reviews and longitudinal studies published between 2007 and 2015 |
| Asthma development | **Sufficient evidence of an association:** Wheeze, Limited or suggestive evidence of an association: Lower respiratory illness in otherwise healthy children | **Sufficient evidence of an association:** Asthma development, Wheeze, Current asthma | **Sufficient evidence of a causal relationship:** in relation to damp and mouldy workplaces |
| Asthma exacerbation | **Sufficient evidence of an association:** Asthma symptoms in sensitized asthmatic persons | **Sufficient evidence of an association** | **Sufficient evidence of an association** in general population |
| Allergic rhinitis | Not evaluated individually | **Sufficient evidence of an association:** Upper respiratory tract symptoms, Limited or suggestive evidence: Allergic rhinitis | **Sufficient evidence of an association** |
| Other respiratory effects | **Sufficient evidence of an association:** Hypersensitivity pneumonitis in susceptible persons, Cough, Limited or insufficient evidence of an association: Dyspnoea (shortness of breath), Airflow obstruction (in otherwise healthy persons), Mucous membrane irritation syndrome, Chronic obstructive pulmonary disease, Inhalation fevers (non-occupational exposures) | **Sufficient evidence of an association:** Cough, Dyspnoea, Respiratory infections | Not evaluated individually |

**Sufficient Evidence of a Causal Relationship**: Evidence is sufficient to conclude that a causal relationship exists between the agent and the outcome. That is, the evidence fulfills the criteria for "sufficient evidence of an association" and, in addition, satisfies the following criteria: strength of association, biologic gradient, consistency of association, biologic plausibility and coherence, and temporally correct association.

**Sufficient Evidence of an Association**: Evidence is sufficient to conclude that there is an association. That is, an association between the agent and the outcome has been observed in studies in which chance, bias, and confounding can be ruled out with reasonable confidence.

**Limited or Suggestive Evidence of an Association**: Evidence is suggestive of an association between the agent and the outcome but is limited because chance, bias, and confounding cannot be ruled out with confidence.

**Inadequate or Insufficient Evidence to Determine Whether an Association Exists**: The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence of an association. Alternatively, no studies exist that examine the relationship.
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