ON LINE SUPPLEMENT

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 1st Tertile: 1 (ref) 2nd tertile 0.78 [0.40-1.55] 3rd tertile 0.42 [0.18-0.99] Persistent wheeze 1st Tertile: 1 (ref) 2nd tertile 1.07 [0.53-2.16] 3rd tertile 0.37 [0.15-0.96]
Iossifova USA (113)	Birth cohort CCAPS n=574	Main living quarter floor dust glucans at 8 months	Recurrent wheeze (13 months)	Glucans low vs high: quartile 1 vs 4 Q1 <22 µg/g aOR 3.04 [1,25-7,38] Q4 >133 µg/g aOR 0.39 [0,16-0,93]
Iossifova USA (114)	Birth cohort CCAPS n=483	Idem	Asthma predictive index (3 years)	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 Netherland (115)	(678) Nested Case Control	LR floor and bedroom mattress dust EPS Glucans	DD asthma (6 years)	EPS: 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)	Glucans NS ERMI ≥5.2 vs < 5.2 : aOR 2.6 [1.1-6.26]
Reponen USA : (116)	Birth cohort CCAPS n=289	Idem	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 (41)	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 Behbold 2013+ indoor airborne moulds (CFU/m^3)	Current asthma (13 years)	Dust *yeasts* HR=0.86 [0.75-0.98] Airborne *Alternaria* Q4 ≥ *11.1 vs <11.1 CFU/* m^3 :HR 1.70 [1.01-2.86]
Tisher 2016 (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	Bedroom wall (electrostatic dust cloth) for 4 weeks qPCR moulds	1<Children<7 years Incident wheezing	No relationship with qPCR

CCAPS: Cincinnatti 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

<table>
<tr><th>References</th><th>Study design</th><th>Mould exposure</th><th>Main outcomes</th><th>Results</th></tr>
<tr>
<td>Jaakkola
2006
Finland
(36)</td>
<td>Population-based incident case-control study
n= 521 new asthma cases / n=932 controls (21-63 years old)</td>
<td>Questionnaire data on visible mould, and mould odour at home and indoors at work</td>
<td>Diagnosed asthma defined as the occurrence of at least one asthma-like symptom and reversible airways obstruction in lung function</td>
<td>Adjusted OR for incident asthma
with reference = no mould, no carpet
<table>
<tr><td></td><td>aOR, 95% CI</td></tr>
<tr><td>Home environment</td><td></td></tr>
<tr><td>Mould, no carpet</td><td>1.10 (0.76-1.59)</td></tr>
<tr><td>Mould + carpet</td><td>1.51 (0.30-7.64)</td></tr>
<tr><td>Work environment</td><td></td></tr>
<tr><td>Mould, no carpet</td><td>1.39 (0.91-2.13)</td></tr>
<tr><td>Mould + carpet</td><td>4.64 (1.11-19.4)</td></tr>
</table>
</td>
</tr>
<tr>
<td>Gunnbjörnsdóttir
2006
Iceland, Norway, Sweden, Denmark, and Estonia
(37)</td>
<td>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</td>
<td><u>Cross sectional analysis</u>
Self-reported water damage or visible mould in the last 12 months.
<u>Longitudinal analysis</u>
Retrospective self-report of any sign of dampness in the home since the baseline survey.</td>
<td>Prevalence, incidence and remission of respiratory symptoms and asthma</td>
<td>OR for respiratory symptoms in subjects living in damp housing since the baseline survey
<table>
<tr><td></td><td>incidence</td></tr>
<tr><td>wheeze</td><td>1.28 (1.12-1.46)</td></tr>
<tr><td>nocturnal breathlessness</td><td>1.33 (1.09-1.63)</td></tr>
<tr><td>nocturnal cough</td><td>1.26 (1.13-1.41)</td></tr>
<tr><td>asthma</td><td>1.13 (0.92-1.40)</td></tr>
<tr><td></td><td>remission</td></tr>
<tr><td>wheeze</td><td>0.88 (0.74-1.03)</td></tr>
<tr><td>nocturnal breathlessness</td><td>0.68 (0.48-0.96)</td></tr>
<tr><td>nocturnal cough</td><td>0.84 (0.73-0.97)</td></tr>
<tr><td>asthma</td><td>0.65 (0.36-1.17)</td></tr>
</table>
</td>
</tr>
<tr>
<td>Norbäck
2011
(38)</td>
<td>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</td>
<td>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.</td>
<td>Longidutinal decline in forced expiratory volume in 1 s (FEV1)</td>
<td>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</td>
</tr>
</table>

<table>
<tr><th>References</th><th>Study design</th><th>Mould exposure</th><th>Main outcomes</th><th>Results</th></tr>
<tr><td></td><td></td><td></td><td></td><td>the dampness score suggesting a dose-response relationship

No significant association in men</td></tr>
<tr><td>Norbäck 2013 (39)</td><td>Population-based longitudinal study Europe (ECRHS I & II) N = 7104 20-45 year-old adults without asthma or asthma-like symptoms at baseline, and followedup after 9 years</td><td>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</td><td>Asthma Incidence

(also consider onset of asthma+bronchial hyperresponsiveness)</td><td>Excess risk of new onset asthma
<table>
<tr><td>Reported Exposure at baseline</td><td>Relative Risk (95%CI)</td></tr>
<tr><td>Water damage 12mo</td><td>1.46 (1.09 to 1.94)</td></tr>
<tr><td>Indoor moulds 12mo</td><td>1.30 (1.00 to 1.68)</td></tr>
<tr><td>Moulds in bedroom (ever)</td><td>1.08 (0.79 to 1.48)</td></tr>
<tr><td>Moulds in living room (ever)</td><td>1.34 (0.91 to 1.97)</td></tr>
<tr><td>Mould score (baseline + follow-up)</td><td></td></tr>
<tr><td>Score 0
Score 1–2
Score 3–4
p for trend</td><td>1 (ref.)
1.05 (0.82 - 1.33)
1.73 (1.27 - 2.37)
0.007</td></tr>
<tr><td>Observed exposure at follow-up</td><td></td></tr>
<tr><td>Any damp spots
Any visible mould</td><td>1.49 (1.00 to 2.22)
1.15 (0.71 to 1.85)</td></tr>
</table>
Stronger effect in those with multisensitisation and in those sensitised to moulds.</td></tr>
</table>

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

<table>
<tr><th>Health Outcomes</th><th>IOM (2004)
Association between health outcomes and the presence of mould or other agents in damp indoor environments
Epidemiological data mainly cross-sectional until 2003</th><th>WHO (2009)
Association between respiratory health outcomes and indoor dampness-related agents
Epidemiological data mainly from cross-sectional studies published between mid-2003 and 2007</th><th colspan="2">ANSES (2016)
Mould exposure and health outcomes
Epidemiological data mainly from meta-analyses, systematic reviews and longitudinal studies published between 2007 and 2015</th></tr>
<tr><td rowspan="2">Asthma development</td><td rowspan="2">Sufficient evidence of an association:
Wheeze
Limited or suggestive evidence of an association :
Lower respiratory illness in otherwise healthy children
Inadequate or insufficient evidence of an association :
Asthma development
Lower respiratory illness in otherwise healthy adults</td><td rowspan="2">Sufficient evidence of an association :
Asthma development
Wheeze
Current asthma
Inadequate or insufficient evidence of an association :
Asthma, ever</td><td><u>Children</u></td><td><u>Adults</u></td></tr>
<tr><td rowspan="2">Sufficient evidence of a causal relationship</td><td rowspan="2">Sufficient evidence of an association :
in relation to damp and mouldy workplaces
Limited evidence of an association :
in general population</td></tr>
<tr><td>Asthma exacerbation</td><td>Sufficient evidence of an association:
Asthma symptoms in sensitized asthmatic persons</td><td>Sufficient evidence of an association</td></tr>
<tr><td>Allergic rhinitis</td><td>Not evaluated individually
Sufficient evidence of an association:
Upper respiratory (nasal and throat) tract symptoms</td><td>Sufficient evidence of an association:
Upper respiratory tract symptoms
Limited or suggestive evidence :
Allergic rhinitis
Inadequate or insufficient evidence of an association :
Allergy or atopy</td><td colspan="2">Sufficient evidence of an association</td></tr>
<tr><td>Other respiratory effects</td><td>Sufficient evidence of an association:
Hypersensitivity pneumonitis in susceptible persons
Cough
Inadequate 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)</td><td>Sufficient evidence of an association :
Cough
Dyspnoea
Respiratory infections
Limited or suggestive evidence of an association :
Bronchitis
Inadequate or insufficient Evidence of an association :
Altered lung function</td><td colspan="2">Not evaluated individually</td></tr>
</table>

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.

REFERENCES

1. Beasley R, Semprini A, Mitchell EA. Risk factors for asthma: is prevention possible? *Lancet* 2015; 386: 1075-1085.
2. Mudarri DH. Valuing the Economic Costs of Allergic Rhinitis, Acute Bronchitis, and Asthma from Exposure to Indoor Dampness and Mold in the US. *J Environ Public Health* 2016; 2016: 2386596.
3. Institute of Medicine National Academic of Science. Damp Indoor Spaces and Health. Washington (DC): National Academies Press; 2004.
4. WHO (World Health Organization). WHO Guidelines for Indoor Air Quality: Dampness and Mould. Geneva; 2009.
5. Antova T, Pattenden S, Brunekreef B, Heinrich J, Rudnai P, Forastiere F, Luttmann-Gibson H, Grize L, Katsnelson B, Moshammer H, Nikiforov B, Slachtova H, Slotova K, Zlotkowska R, Fletcher T. Exposure to indoor mould and children's respiratory health in the PATY study. *J Epidemiol Community Health* 2008; 62: 708-714.
6. Mendell MJ, Mirer AG, Cheung K, Tong M, Douwes J. Respiratory and allergic health effects of dampness, mold, and dampness-related agents: a review of the epidemiologic evidence. *Environ Health Perspect* 2011; 119: 748-756.
7. Tischer C, Chen CM, Heinrich J. Association between domestic mould and mould components, and asthma and allergy in children: a systematic review. *Eur Respir J* 2011; 38: 812-824.
8. Tischer CG, Hohmann C, Thiering E, Herbarth O, Muller A, Henderson J, Granell R, Fantini MP, Luciano L, Bergstrom A, Kull I, Link E, von Berg A, Kuehni CE, Strippoli MP, Gehring U, Wijga A, Eller E, Bindslev-Jensen C, Keil T, Heinrich J, consortium E. Meta-analysis of mould and dampness exposure on asthma and allergy in eight European birth cohorts: an ENRIECO initiative. *Allergy* 2011; 66: 1570-1579.
9. Quansah R, Jaakkola MS, Hugg TT, Heikkinen SA, Jaakkola JJ. Residential dampness and molds and the risk of developing asthma: a systematic review and meta-analysis. *PLoS One* 2012; 7: e47526.
10. Dick S, Friend A, Dynes K, AlKandari F, Doust E, Cowie H, Ayres JG, Turner SW. A systematic review of associations between environmental exposures and development of asthma in children aged up to 9 years. *BMJ Open* 2014; 4: e006554.
11. ANSES. 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.
12. ANSES. Revised opinion of the French Agency for Food, Environmental and Occupational Health and Safety on Mould in buildings. Available on line at: https://www.anses.fr/en/system/files/AIR2014SA0016EN.pdf. 2016.
13. Conseil Supérieur d'Hygiene Publique de France. Contaminations fongiques en milieux intérieurs 2006.
14. Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med* 1965; 58: 295-300.
15. Fisk WJ, Lei-Gomez Q, Mendell MJ. Meta-analyses of the associations of respiratory health effects with dampness and mold in homes. *Indoor Air* 2007; 17: 284-296.
16. Kanchongkittiphon W, Mendell MJ, Gaffin JM, Wang G, Phipatanakul W. Indoor environmental exposures and exacerbation of asthma: an update to the 2000 review by the Institute of Medicine. *Environ Health Perspect* 2015; 123: 6-20.
17. Sharpe RA, Bearman N, Thornton CR, Husk K, Osborne NJ. Indoor fungal diversity and asthma: a meta-analysis and systematic review of risk factors. *J Allergy Clin Immunol* 2015; 135: 110-122.
18. Vesper S, Wymer L. The relationship between environmental relative moldiness index values and asthma. *Int J Hyg Environ Health* 2016; 219: 233-238.

19. Reponen T, Vesper S, Levin L, Johansson E, Ryan P, Burkle J, Grinshpun SA, Zheng S, Bernstein DI, Lockey J, Villareal M, Khurana Hershey GK, LeMasters G. High environmental relative moldiness index during infancy as a predictor of asthma at 7 years of age. *Ann Allergy Asthma Immunol* 2011; 107: 120-126.
20. Pei Zam H, Emilia Z, Karmegam K, Mohd Sapuan S. Dampness and mold exposure in buildings as a risk factor for health effects. *Mal J Pub Health Medicine* 2017; 1 (special issue): 28-40.
21. Hwang BF, Liu IP, Huang TP. Gene-environment interaction between interleukin-4 promoter and molds in childhood asthma. *Ann Epidemiol* 2012; 22: 250-256.
22. Shorter C, Taubel M, Pierse N, Douwes J, Howden-Chapman P, Hyvarinen A, Crane J. Objective assessment of domestic mold contamination using quantitative PCR. *J Allergy Clin Immunol* 2016; 137: 622-624.
23. Zhou C, Baiz N, Zhang T, Banerjee S, Annesi-Maesano I, Group EM-CCS. Modifiable exposures to air pollutants related to asthma phenotypes in the first year of life in children of the EDEN mother-child cohort study. *BMC Public Health* 2013; 13: 506.
24. Wen HJ, Chiang TL, Lin SJ, Guo YL. Predicting risk for childhood asthma by pre-pregnancy, perinatal, and postnatal factors. *Pediatr Allergy Immunol* 2015; 26: 272-279.
25. Karvonen AM, Hyvarinen A, Korppi M, Haverinen-Shaughnessy U, Renz H, Pfefferle PI, Remes S, Genuneit J, Pekkanen J. Moisture damage and asthma: a birth cohort study. *Pediatrics* 2015; 135: e598-606.
26. Thacher JD, Gruzieva O, Pershagen G, Melen E, Lorentzen JC, Kull I, Bergstrom A. Mold and dampness exposure and allergic outcomes from birth to adolescence: data from the BAMSE cohort. *Allergy* 2017; 72: 967-974.
27. Behbod B, Sordillo JE, Hoffman EB, Datta S, Muilenberg ML, Scott JA, Chew GL, Platts-Mills TA, Schwartz J, Burge H, Gold DR. Wheeze in infancy: protection associated with yeasts in house dust contrasts with increased risk associated with yeasts in indoor air and other fungal taxa. *Allergy* 2013; 68: 1410-1418.
28. Behbod B, Sordillo JE, Hoffman EB, Datta S, Webb TE, Kwan DL, Kamel JA, Muilenberg ML, Scott JA, Chew GL, Platts-Mills TA, Schwartz J, Coull B, Burge H, Gold DR. Asthma and allergy development: contrasting influences of yeasts and other fungal exposures. *Clin Exp Allergy* 2015; 45: 154-163.
29. Rosenbaum PF, Crawford JA, Anagnost SE, Wang CJ, Hunt A, Anbar RD, Hargrave TM, Hall EG, Liu CC, Abraham JL. Indoor airborne fungi and wheeze in the first year of life among a cohort of infants at risk for asthma. *J Expo Sci Environ Epidemiol* 2010; 20: 503-515.
30. Dannemiller KC, Mendell MJ, Macher JM, Kumagai K, Bradman A, Holland N, Harley K, Eskenazi B, Peccia J. Next-generation DNA sequencing reveals that low fungal diversity in house dust is associated with childhood asthma development. *Indoor Air* 2014; 24: 236-247.
31. Tischer C, Weikl F, Probst AJ, Standl M, Heinrich J, Pritsch K. Urban Dust Microbiome: Impact on Later Atopy and Wheezing. *Environ Health Perspect* 2016; 124: 1919-1923.
32. Wu AC, Lasky-Su J, Rogers CA, Klanderman BJ, Litonjua AA. Fungal exposure modulates the effect of polymorphisms of chitinases on emergency department visits and hospitalizations. *Am J Respir Crit Care Med* 2010; 182: 884-889.
33. Vicendese D, Dharmage SC, Tang ML, Olenko A, Allen KJ, Abramson MJ, Erbas B. Bedroom air quality and vacuuming frequency are associated with repeat child asthma hospital admissions. *J Asthma* 2015; 52: 727-731.
34. Dannemiller KC, Gent JF, Leaderer BP, Peccia J. Indoor microbial communities: Influence on asthma severity in atopic and nonatopic children. *J Allergy Clin Immunol* 2016; 138: 76-83 e71.
35. Casas L, Espinosa A, Pekkanen J, Asikainen A, Borras-Santos A, Jacobs J, Krop EJ, Taubel M, Hyvarinen A, Heederik D, Zock JP. School attendance and daily respiratory symptoms in children: influence of moisture damage. *Indoor Air* 2017; 27: 303-310.
36. Jaakkola JJ, Ieromnimon A, Jaakkola MS. Interior surface materials and asthma in adults: a population-based incident case-control study. *Am J Epidemiol* 2006; 164: 742-749.

37. Gunnbjornsdottir MI, Franklin KA, Norback D, Bjornsson E, Gislason D, Lindberg E, Svanes C, Omenaas E, Norrman E, Jogi R, Jensen EJ, Dahlman-Hoglund A, Janson C, Group RS. Prevalence and incidence of respiratory symptoms in relation to indoor dampness: the RHINE study. *Thorax* 2006; 61: 221-225.
38. Norback D, Zock JP, Plana E, Heinrich J, Svanes C, Sunyer J, Kunzli N, Villani S, Olivieri M, Soon A, Jarvis D. Lung function decline in relation to mould and dampness in the home: the longitudinal European Community Respiratory Health Survey ECRHS II. *Thorax* 2011; 66: 396-401.
39. Norback D, Zock JP, Plana E, Heinrich J, Svanes C, Sunyer J, Kunzli N, Villani S, Olivieri M, Soon A, Jarvis D. Mould and dampness in dwelling places, and onset of asthma: the population-based cohort ECRHS. *Occup Environ Med* 2013; 70: 325-331.
40. Jaakkola MS, Nordman H, Piipari R, Uitti J, Laitinen J, Karjalainen A, Hahtola P, Jaakkola JJ. Indoor dampness and molds and development of adult-onset asthma: a population-based incident case-control study. *Environ Health Perspect* 2002; 110: 543-547.
41. Piipari R, Keskinen H. Agents causing occupational asthma in Finland in 1986-2002: cow epithelium bypassed by moulds from moisture-damaged buildings. *Clin Exp Allergy* 2005; 35: 1632-1637.
42. Karvala K, Toskala E, Luukkonen R, Lappalainen S, Uitti J, Nordman H. New-onset adult asthma in relation to damp and moldy workplaces. *Int Arch Occup Environ Health* 2010; 83: 855-865.
43. Karvala K, Toskala E, Luukkonen R, Uitti J, Lappalainen S, Nordman H. Prolonged exposure to damp and moldy workplaces and new-onset asthma. *Int Arch Occup Environ Health* 2011; 84: 713-721.
44. Karvala K, Uitti J, Luukkonen R, Nordman H. Quality of life of patients with asthma related to damp and moldy work environments. *Scand J Work Environ Health* 2013; 39: 96-105.
45. Karvala K, Nordman H, Luukkonen R, Uitti J. Asthma related to workplace dampness and impaired work ability. *Int Arch Occup Environ Health* 2014; 87: 1-11.
46. Park JH, Cox-Ganser JM, Kreiss K, White SK, Rao CY. Hydrophilic fungi and ergosterol associated with respiratory illness in a water-damaged building. *Environ Health Perspect* 2008; 116: 45-50.
47. Park JH, Kreiss K, Cox-Ganser JM. Rhinosinusitis and mold as risk factors for asthma symptoms in occupants of a water-damaged building. *Indoor Air* 2012; 22: 396-404.
48. Jaakkola MS, Quansah R, Hugg TT, Heikkinen SA, Jaakkola JJ. Association of indoor dampness and molds with rhinitis risk: a systematic review and meta-analysis. *J Allergy Clin Immunol* 2013; 132: 1099-1110 e1018.
49. Szefler SJ, Wenzel S, Brown R, Erzurum SC, Fahy JV, Hamilton RG, Hunt JF, Kita H, Liu AH, Panettieri RA, Jr., Schleimer RP, Minnicozzi M. Asthma outcomes: biomarkers. *J Allergy Clin Immunol* 2012; 129: S9-23.
50. Vijverberg SJ, Hilvering B, Raaijmakers JA, Lammers JW, Maitland-van der Zee AH, Koenderman L. Clinical utility of asthma biomarkers: from bench to bedside. *Biologics* 2013; 7: 199-210.
51. Casale TB. Biologics and biomarkers for asthma, urticaria, and nasal polyposis. *J Allergy Clin Immunol* 2017; 139: 1411-1421.
52. Kelly RS, Dahlin A, McGeachie MJ, Qiu W, Sordillo J, Wan ES, Wu AC, Lasky-Su J. Asthma Metabolomics and the Potential for Integrative Omics in Research and the Clinic. *Chest* 2017; 151: 262-277.
53. Reponen T, Seo SC, Grimsley F, Lee T, Crawford C, Grinshpun SA. Fungal Fragments in Moldy Houses: A Field Study in Homes in New Orleans and Southern Ohio. *Atmos Environ (1994)* 2007; 41: 8140-8149.
54. Korpi A, Jarnberg J, Pasanen AL. Microbial volatile organic compounds. *Crit Rev Toxicol* 2009; 39: 139-193.
55. Moularat S, Robine E, Ramalho O, Oturan MA. Detection of fungal development in a closed environment through the identification of specific VOC: demonstration of a specific VOC fingerprint for fungal development. *Sci Total Environ* 2008; 407: 139-146.

56. Wong J, Magun BE, Wood LJ. Lung inflammation caused by inhaled toxicants: a review. *Int J Chron Obstruct Pulmon Dis* 2016; 11: 1391-1401.
57. Zock JP, Heinrich J, Jarvis D, Verlato G, Norback D, Plana E, Sunyer J, Chinn S, Olivieri M, Soon A, Villani S, Ponzio M, Dahlman-Hoglund A, Svanes C, Luczynska C, Indoor Working Group of the European Community Respiratory Health S, II. Distribution and determinants of house dust mite allergens in Europe: the European Community Respiratory Health Survey II. *J Allergy Clin Immunol* 2006; 118: 682-690.
58. von Mutius E, Braun-Fahrlander C, Schierl R, Riedler J, Ehlermann S, Maisch S, Waser M, Nowak D. Exposure to endotoxin or other bacterial components might protect against the development of atopy. *Clin Exp Allergy* 2000; 30: 1230-1234.
59. Caillaud D, Evrard B, Laurichesse H, Souweine B. [Role of indoor endotoxins in asthma symptoms]. *Revue des maladies respiratoires* 2009; 26: 893-899.
60. Thorne PS, Mendy A, Metwali N, Salo P, Co C, Jaramillo R, Rose KM, Zeldin DC. Endotoxin Exposure: Predictors and Prevalence of Associated Asthma Outcomes in the United States. *Am J Respir Crit Care Med* 2015; 192: 1287-1297.
61. Mustonen K, Karvonen AM, Kirjavainen P, Roponen M, Schaub B, Hyvarinen A, Frey U, Renz H, Pfefferle PI, Genuneit J, Vaarala O, Pekkanen J. Moisture damage in home associates with systemic inflammation in children. *Indoor Air* 2016; 26: 439-447.
62. Nevalainen A, Taubel M, Hyvarinen A. Indoor fungi: companions and contaminants. *Indoor Air* 2015; 25: 125-156.
63. Mendell MJ, Kumagai K. Observation-based metrics for residential dampness and mold with dose-response relationships to health: A review. *Indoor Air* 2017; 27: 506-517.
64. Hyvarinen A, Vahteristo M, Meklin T, Jantunen M, Nevalainen A, Moschandreas D. Temporal and spatial variation of fungal concentrations in indoor air. *Aerosol Sci Technnol* 2001; 35: 688-695.
65. Frankel M, Timm M, Hansen EW, Madsen AM. Comparison of sampling methods for the assessment of indoor microbial exposure. *Indoor Air* 2012; 22: 405-414.
66. Alanio A, Bretagne S. Difficulties with molecular diagnostic tests for mould and yeast infections: where do we stand? *Clin Microbiol Infect* 2014; 20 Suppl 6: 36-41.
67. Vesper S, McKinstry C, Haugland R, Wymer L, Bradham K, Ashley P, Cox D, Dewalt G, Friedman W. Development of an Environmental Relative Moldiness index for US homes. *J Occup Environ Med* 2007; 49: 829-833.
68. Taubel M, Karvonen AM, Reponen T, Hyvarinen A, Vesper S, Pekkanen J. Application of the Environmental Relative Moldiness Index in Finland. *Appl Environ Microbiol* 2016; 82: 578-584.
69. Hilton SK, Castro-Nallar E, Perez-Losada M, Toma I, McCaffrey TA, Hoffman EP, Siegel MO, Simon GL, Johnson WE, Crandall KA. Metataxonomic and Metagenomic Approaches vs. Culture-Based Techniques for Clinical Pathology. *Front Microbiol* 2016; 7: 484.
70. Karvonen AM, Hyvarinen A, Rintala H, Korppi M, Taubel M, Doekes G, Gehring U, Renz H, Pfefferle PI, Genuneit J, Keski-Nisula L, Remes S, Lampi J, von Mutius E, Pekkanen J. Quantity and diversity of environmental microbial exposure and development of asthma: a birth cohort study. *Allergy* 2014; 69: 1092-1101.
71. Brooks C, Pearce N, Douwes J. The hygiene hypothesis in allergy and asthma: an update. *Curr Opin Allergy Clin Immunol* 2013; 13: 70-77.
72. Rook GA. Regulation of the immune system by biodiversity from the natural environment: an ecosystem service essential to health. *Proc Natl Acad Sci U S A* 2013; 110: 18360-18367.
73. Stein MM, Hrusch CL, Gozdz J, Igartua C, Pivniouk V, Murray SE, Ledford JG, Marques dos Santos M, Anderson RL, Metwali N, Neilson JW, Maier RM, Gilbert JA, Holbreich M, Thorne PS, Martinez FD, von Mutius E, Vercelli D, Ober C, Sperling AI. Innate Immunity and Asthma Risk in Amish and Hutterite Farm Children. *N Engl J Med* 2016; 375: 411-421.

74. Birzele LT, Depner M, Ege MJ, Engel M, Kublik S, Bernau C, Loss GJ, Genuneit J, Horak E, Schloter M, Braun-Fahrlander C, Danielewicz H, Heederik D, von Mutius E, Legatzki A. Environmental and mucosal microbiota and their role in childhood asthma. *Allergy* 2016.
75. Shelton BG, Kirkland KH, Flanders WD, Morris GK. Profiles of airborne fungi in buildings and outdoor environments in the United States. *Appl Environ Microbiol* 2002; 68: 1743-1753.
76. Caillaud DM, Martin S, Segala C, Vidal P, Lecadet J, Pellier S, Rouzaire P, Tridon A, Evrard B. Airborne pollen levels and drug consumption for seasonal allergic rhinoconjunctivitis: a 10-year study in France. *Allergy* 2015; 70: 99-106.
77. Madureira J, Paciencia I, Cavaleiro-Rufo J, de Oliveira Fernandes E. Indoor pollutant exposure among children with and without asthma in Porto, Portugal, during the cold season. *Environ Sci Pollut Res Int* 2016; 23: 20539-20552.
78. Rocchi S, Reboux G, Frossard V, Scherer E, Valot B, Laboissiere A, Zaros C, Vacheyrou M, Gillet F, Roussel S, Raherison C, Millon L, Elfe t. Microbiological characterization of 3193 French dwellings of Elfe cohort children. *Sci Total Environ* 2015; 505: 1026-1035.
79. Burr ML, Matthews IP, Arthur RA, Watson HL, Gregory CJ, Dunstan FD, Palmer SR. Effects on patients with asthma of eradicating visible indoor mould: a randomised controlled trial. *Thorax* 2007; 62: 767-772.
80. Semple S, Garden C, Coggins M, Galea KS, Whelan P, Cowie H, Sanchez-Jimenez A, Thorne PS, Hurley JF, Ayres JG. Contribution of solid fuel, gas combustion, or tobacco smoke to indoor air pollutant concentrations in Irish and Scottish homes. *Indoor Air* 2012; 22: 212-223.
81. Adams RI, Miletto M, Lindow SE, Taylor JW, Bruns TD. Airborne bacterial communities in residences: similarities and differences with fungi. *PLoS One* 2014; 9: e91283.
82. Amend AS, Seifert KA, Samson R, Bruns TD. Indoor fungal composition is geographically patterned and more diverse in temperate zones than in the tropics. *Proc Natl Acad Sci U S A* 2010; 107: 13748-13753.
83. Sharpe R, Thornton CR, Osborne NJ. Modifiable factors governing indoor fungal diversity and risk of asthma. *Clin Exp Allergy* 2014; 44: 631-641.
84. Meyers DA, Bleecker ER, Holloway JW, Holgate ST. Asthma genetics and personalised medicine. *Lancet Respir Med* 2014; 2: 405-415.
85. Rava M, Smit LA, Nadif R. Gene-environment interactions in the study of asthma in the postgenomewide association studies era. *Curr Opin Allergy Clin Immunol* 2015; 15: 70-78.
86. Osborne NJ, Thornton CR, Sharpe RA. Indoor Fungal Exposure and Allergic Respiratory Disease. *Curr Allergy Asthma Rep* 2015; 15: 71.
87. Bush RK, Portnoy JM, Saxon A, Terr AI, Wood RA. The medical effects of mold exposure. *J Allergy Clin Immunol* 2006; 117: 326-333.
88. Sharpe RA, Thornton CR, Tyrrell J, Nikolaou V, Osborne NJ. Variable risk of atopic disease due to indoor fungal exposure in NHANES 2005-2006. *Clin Exp Allergy* 2015; 45: 1566-1578.
89. Zhang Z, Reponen T, Hershey GK. Fungal Exposure and Asthma: IgE and Non-IgE-Mediated Mechanisms. *Curr Allergy Asthma Rep* 2016; 16: 86.
90. Miller JD, McMullin DR. Fungal secondary metabolites as harmful indoor air contaminants: 10 years on. *Appl Microbiol Biotechnol* 2014; 98: 9953-9966.
91. Zhang Z, Biagini Myers JM, Brandt EB, Ryan PH, Lindsey M, Mintz-Cole RA, Reponen T, Vesper SJ, Forde F, Ruff B, Bass SA, LeMasters GK, Bernstein DI, Lockey J, Budelsky AL, Khurana Hershey GK. beta-Glucan exacerbates allergic asthma independent of fungal sensitization and promotes steroid-resistant TH2/TH17 responses. *J Allergy Clin Immunol* 2017; 139: 54-65 e58.
92. Crameri R, Garbani M, Rhyner C, Huitema C. Fungi: the neglected allergenic sources. *Allergy* 2014; 69: 176-185.
93. Twaroch TE, Curin M, Valenta R, Swoboda I. Mold allergens in respiratory allergy: from structure to therapy. *Allergy Asthma Immunol Res* 2015; 7: 205-220.

94. Krieger J, Jacobs DE, Ashley PJ, Baeder A, Chew GL, Dearborn D, Hynes HP, Miller JD, Morley R, Rabito F, Zeldin DC. Housing interventions and control of asthma-related indoor biologic agents: a review of the evidence. *J Public Health Manag Pract* 2010; 16: S11-20.
95. Sauni R, Verbeek JH, Uitti J, Jauhiainen M, Kreiss K, Sigsgaard T. Remediating buildings damaged by dampness and mould for preventing or reducing respiratory tract symptoms, infections and asthma. *Cochrane Database Syst Rev* 2015: CD007897.
96. Le Cann P, Paulus H, Glorennec P, Le Bot B, Frain S, Gangneux JP. Home Environmental Interventions for the Prevention or Control of Allergic and Respiratory Diseases: What Really Works. *J Allergy Clin Immunol Pract* 2017; 5: 66-79.
97. Lajoie P, Aubin D, Gingras V, Daigneault P, Ducharme F, Gauvin D, Fugler D, Leclerc JM, Won D, Courteau M, Gingras S, Heroux ME, Yang W, Schleibinger H. The IVAIRE project--a randomized controlled study of the impact of ventilation on indoor air quality and the respiratory symptoms of asthmatic children in single family homes. *Indoor Air* 2015; 25: 582-597.
98. Pekkanen J, Hyvarinen A, Haverinen-Shaughnessy U, Korppi M, Putus T, Nevalainen A. Moisture damage and childhood asthma: a population-based incident case-control study. *Eur Respir J* 2007; 29: 509-515.
99. Karvonen AM, Hyvarinen A, Roponen M, Hoffmann M, Korppi M, Remes S, von Mutius E, Nevalainen A, Pekkanen J. Confirmed moisture damage at home, respiratory symptoms and atopy in early life: a birth-cohort study. *Pediatrics* 2009; 124: e329-338.
100. Schroer KT, Biagini Myers JM, Ryan PH, LeMasters GK, Bernstein DI, Villareal M, Lockey JE, Reponen T, Grinshpun S, Khurana Hershey GK. Associations between multiple environmental exposures and Glutathione S-Transferase P1 on persistent wheezing in a birth cohort. *J Pediatr* 2009; 154: 401-408, 408 e401.
101. Dales R, Ruest K, Guay M, Marro L, David Miller J. Residential fungal growth and incidence of acute respiratory illness during the first two years of life. *Environ Res* 2010; 110: 692-698.
102. Larsson M, Hagerhed-Engman L, Moniruzzaman S, Janson S, Sundell J, Bornehag CG. Can we trust cross-sectional studies when studying the risk of moisture-related problems indoor for asthma in children? *Int J Environ Health Res* 2011; 21: 237-247.
103. Hwang BF, Liu IP, Huang TP. Molds, parental atopy and pediatric incident asthma. *Indoor Air* 2011; 21: 472-478.
104. Hagmolen of Ten Have W, van den Berg NJ, van der Palen J, van Aalderen WM, Bindels PJ. Residential exposure to mould and dampness is associated with adverse respiratory health. *Clin Exp Allergy* 2007; 37: 1827-1832.
105. Inal A, Karakoc GB, Altintas DU, Guvenmez HK, Aka Y, Gelisken R, Yilmaz M, Kendirli SG. Effect of indoor mold concentrations on daily symptom severity of children with asthma and/or rhinitis monosensitized to molds. *J Asthma* 2007; 44: 543-546.
106. Bundy KW, Gent JF, Beckett W, Bracken MB, Belanger K, Triche E, Leaderer BP. Household airborne Penicillium associated with peak expiratory flow variability in asthmatic children. *Ann Allergy Asthma Immunol* 2009; 103: 26-30.
107. Pongracic JA, O'Connor GT, Muilenberg ML, Vaughn B, Gold DR, Kattan M, Morgan WJ, Gruchalla RS, Smartt E, Mitchell HE. Differential effects of outdoor versus indoor fungal spores on asthma morbidity in inner-city children. *J Allergy Clin Immunol* 2010; 125: 593-599.
108. Gent JF, Kezik JM, Hill ME, Tsai E, Li DW, Leaderer BP. Household mold and dust allergens: exposure, sensitization and childhood asthma morbidity. *Environ Res* 2012; 118: 86-93.
109. Biagini JM, LeMasters GK, Ryan PH, Levin L, Reponen T, Bernstein DI, Villareal M, Khurana Hershey GK, Burkle J, Lockey J. Environmental risk factors of rhinitis in early infancy. *Pediatr Allergy Immunol* 2006; 17: 278-284.
110. Osborne M, Reponen T, Adhikari A, Cho SH, Grinshpun SA, Levin L, Bernstein DI, LeMasters G. Specific fungal exposures, allergic sensitization, and rhinitis in infants. *Pediatr Allergy Immunol* 2006; 17: 450-457.

111. Jaakkola JJ, Hwang BF, Jaakkola MS. Home dampness and molds as determinants of allergic rhinitis in childhood: a 6-year, population-based cohort study. *Am J Epidemiol* 2010; 172: 451-459.
112. Douwes J, van Strien R, Doekes G, Smit J, Kerkhof M, Gerritsen J, Postma D, de Jongste J, Travier N, Brunekreef B. Does early indoor microbial exposure reduce the risk of asthma? The Prevention and Incidence of Asthma and Mite Allergy birth cohort study. *J Allergy Clin Immunol* 2006; 117: 1067-1073.
113. Iossifova YY, Reponen T, Bernstein DI, Levin L, Kalra H, Campo P, Villareal M, Lockey J, Hershey GK, LeMasters G. House dust (1-3)-beta-D-glucan and wheezing in infants. *Allergy* 2007; 62: 504-513.
114. Iossifova YY, Reponen T, Ryan PH, Levin L, Bernstein DI, Lockey JE, Hershey GK, Villareal M, LeMasters G. Mold exposure during infancy as a predictor of potential asthma development. *Ann Allergy Asthma Immunol* 2009; 102: 131-137.
115. Tischer C, Gehring U, Chen CM, Kerkhof M, Koppelman G, Sausenthaler S, Herbarth O, Schaaf B, Lehmann I, Kramer U, Berdel D, von Berg A, Bauer CP, Koletzko S, Wichmann HE, Brunekreef B, Heinrich J. Respiratory health in children, and indoor exposure to (1,3)-beta-D-glucan, EPS mould components and endotoxin. *Eur Respir J* 2011; 37: 1050-1059.
116. Reponen T, Lockey J, Bernstein DI, Vesper SJ, Levin L, Khurana Hershey GK, Zheng S, Ryan P, Grinshpun SA, Villareal M, Lemasters G. Infant origins of childhood asthma associated with specific molds. *J Allergy Clin Immunol* 2012; 130: 639-644 e635.