



Asma bronchiale da irritanti

23 Novembre 2019

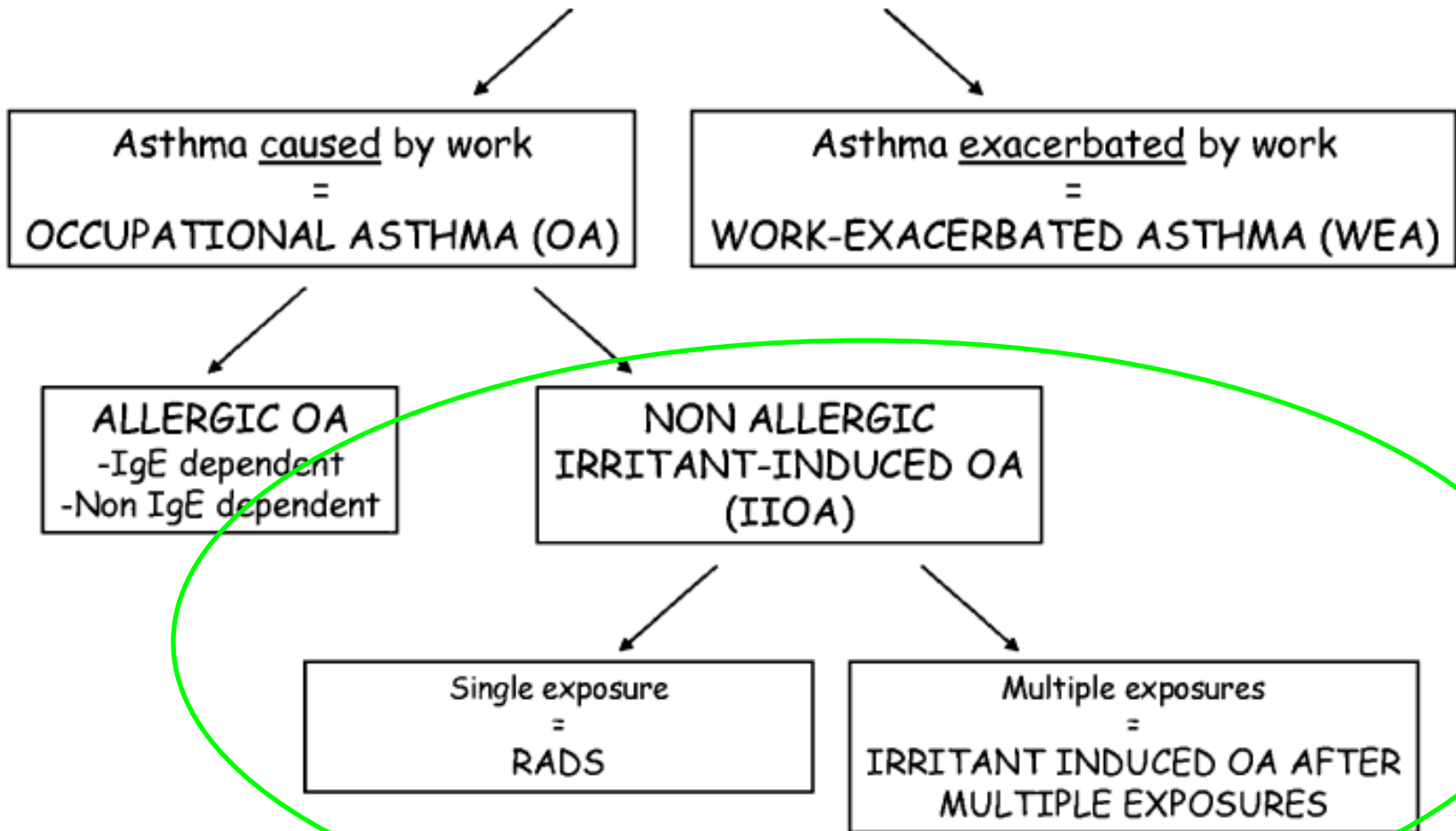
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WORK-RELATED ASTHMA





Do chronic workplace irritant exposures cause asthma?

Orianne Dumas^{a,b} and Nicole Le Moual^{a,b}

Curr Opin Allergy Clin Immunol 2016, 16:75–85

Purpose of review

The present review summarizes the recent literature on the relation between chronic workplace irritant

Si stima che fino al 20% dei casi di asma correlata con il lavoro sia da attribuirsi all'esposizione ad **agenti inalanti irritanti**

(Labreque 2012, Brooks 2014)

recent epidemiological studies strengthen the evidence of an effect of chronic exposure to irritants in work-related asthma. The underlying mechanism remains unknown but may be related to oxidative stress, neurogenic inflammation and dual irritant and adjuvant effects. However, disentangling chronic irritant effects from either acute irritant-induced asthma or immunological low molecular weight agent-induced asthma is difficult for some agents. Further research is needed to improve assessment of irritant exposures and identify biomarkers.

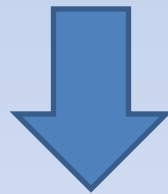
Keywords

cleaning agents, disinfectants, irritant-induced asthma, workplace exposures

Il termine di *Asma Indotta da Irritanti* è stato introdotto per indicare lo sviluppo di:

- sintomi d'asma (respiro sibilante, dispnea, costrizione toracica e tosse)
- iperreattività bronchiale aspecifica
- infiammazione delle vie aeree

Consequente all'esposizione lavorativa ad agenti inalanti irritanti



Asma professionale
meccanismo non immunologico/allergologico

Table 2. Features of various forms of work related asthma⁵

	Work exacerbated asthma	Sensitiser induced occupational asthma	Irritant induced occupational asthma
Symptoms of asthma	Yes	Yes	Yes
Onset	Before or during working life	Onset or recurrence during working life. Usually first develops some weeks to months after first exposure	Usually within 24 hours of exposure to large quantity of respiratory irritant
Relation to work schedule	Worse on one or more days while at work	Symptoms worse during or after a work shift and improve when away from work	Often none
Other	Exposure at work to asthma exacerbating factors such as dust, smoke, fumes, cold	Exposure to a known sensitiser	Persistence of symptoms for at least 12 weeks, but no previously documented asthma or chronic lung disease

Work related asthma, M.J. Abramson et al. 2010

Table 1 Diagnostic criteria for acute-onset irritant-induced asthma*

- 1 Absence of preexisting asthma symptomatology
 - 2 Onset of asthma symptoms after a single specific inhalational exposure or accident
 - 3 Exposure to an irritant vapor, gas, fume, or smoke in very high concentration
 - 4 Onset of asthma symptoms within minutes to hours and <24 h after the exposure
 - 5 Presence of airflow limitation with a significant bronchodilator response or nonspecific bronchial hyperresponsiveness to histamine/methacholine
 - 6 Exclusion of other pulmonary disorders that can explain the symptoms or simulate asthma
-

*The diagnostic criteria for Reactive Airways Dysfunction Syndrome have been adapted from Brooks et al. (9, 21) and the American College of Chest Physicians guidelines (4).

Table 2. Features of Irritant-Induced Occupational Asthma.

Criteria for RADS*	Modifications to Criteria for RADS†
History of new-onset asthma	History of new-onset asthma or recurrence of childhood asthma
Symptom onset related to a single high-level exposure (usually accidental)	Symptom onset related to one or more high-level exposures
Onset of symptoms ≤ 24 hr after exposure	Symptoms can begin >24 hr (in some reports, up to several days) after exposure
Exposure to a very high concentration of gas, fume, or spray with known irritant properties	List of exposures includes highly irritating dust (e.g., after the World Trade Center collapse)
Airway hyperresponsiveness or reversible airflow obstruction	
Symptoms persistent for ≥ 3 mo	
No previous lower respiratory tract symptoms	Previous airway disease associated with smoking or atopy may be difficult to rule out

* The criteria for the reactive airways dysfunction syndrome (RADS) were adapted from Brooks et al.¹⁸

† Patients were considered to have irritant-induced asthma in some studies with one or more of these modified criteria.^{6,19-21}

**Susan M.Tarlo. Irritant induced asthma in the workplace,
Current Allergy and asthma reports, 2014**

RADS	ASMA INDOTTA DA IRRITANTI
Storia di asma di nuova insorgenza	Storia di asma di nuova insorgenza o recidiva di asma infantile
Insorgenza dei sintomi dopo una singola esposizione accidentale ad alti livelli	Insorgenza dei sintomi dopo una o più esposizioni ad alti livelli
Inizio dei sintomi entro 24 ore dall'esposizione	Inizio dei sintomi anche oltre 24 ore dall'esposizione (in alcuni casi anche dopo diversi giorni)
Esposizione ad una concentrazione molto elevata di un gas, fumo o vapore con proprietà irritanti note	L'elenco delle esposizioni comprende anche polveri altamente irritanti (crollo Torri Gemelle)
Iperresponsività delle vie aeree o ostruzione bronchiale al flusso aereo	
Persistenza dei sintomi per almeno 3 mesi	
Nessun precedente sintomo del tratto respiratorio inferiore	Può essere difficile escludere la presenza di precedenti malattie polmonari associate a fumo o atopia

**Susan M.Tarlo. Irritant induced asthma in the workplace,
Current Allergy and asthma reports, 2014**

POSITION PAPER

EAACI position paper: irritant-induced asthma

O. Vandенplас¹, M. Wiszniewska², M. Raulf³, F. de Blay⁴, R. Gerth van Wijk⁵, G. Moscato⁶, B. Nemery⁷, G. Pala⁸, S. Quirce⁹, J. Sastre¹⁰, V. Schlünssen¹¹, T. Sigsgaard¹¹, A. Siracusa¹², S. M. Tarlo^{13,14,15}, V. van Kampen³, J.-P. Zock^{16,17,18,19} & J. Walusiak-Skorupa²

- **Classificazione operativa**
- **Algoritmo pratico- diagnostico basato su:**
 - **Caratteristiche dell'esposizione**
 - **Livello di evidenza a supporto della relazione causale**
 - **Informazioni sull'epidemiologia, sulla patogenesi e sul management dei vari fenotipi di IIA**

Classificazione dell'asma da irritanti (*Irritant Induced Asthma IIA*)

- ***IIA definita*** caratterizzata dall'insorgenza rapida dopo una singola esposizione ad alte concentrazioni di un agente irritante (**RADS**)
- ***IIA probabile*** indotta dall'esposizione multipla ad alte concentrazioni d'irritanti
- ***IIA possibile*** che si manifesta, dopo un periodo di latenza, in seguito all'esposizione a bassi-moderati livelli di agenti irritanti

IRRITANT-INDUCED ASTHMA?

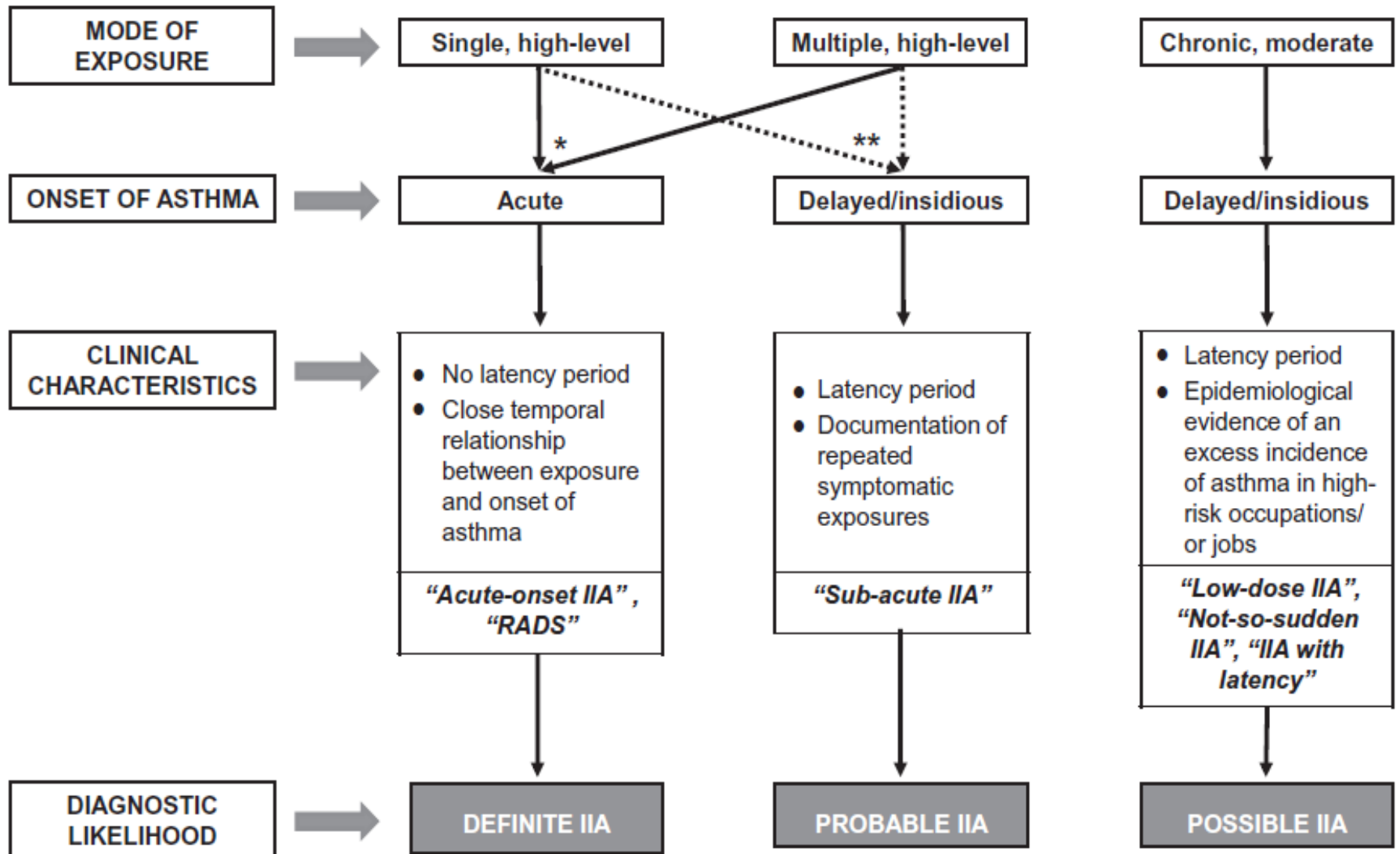
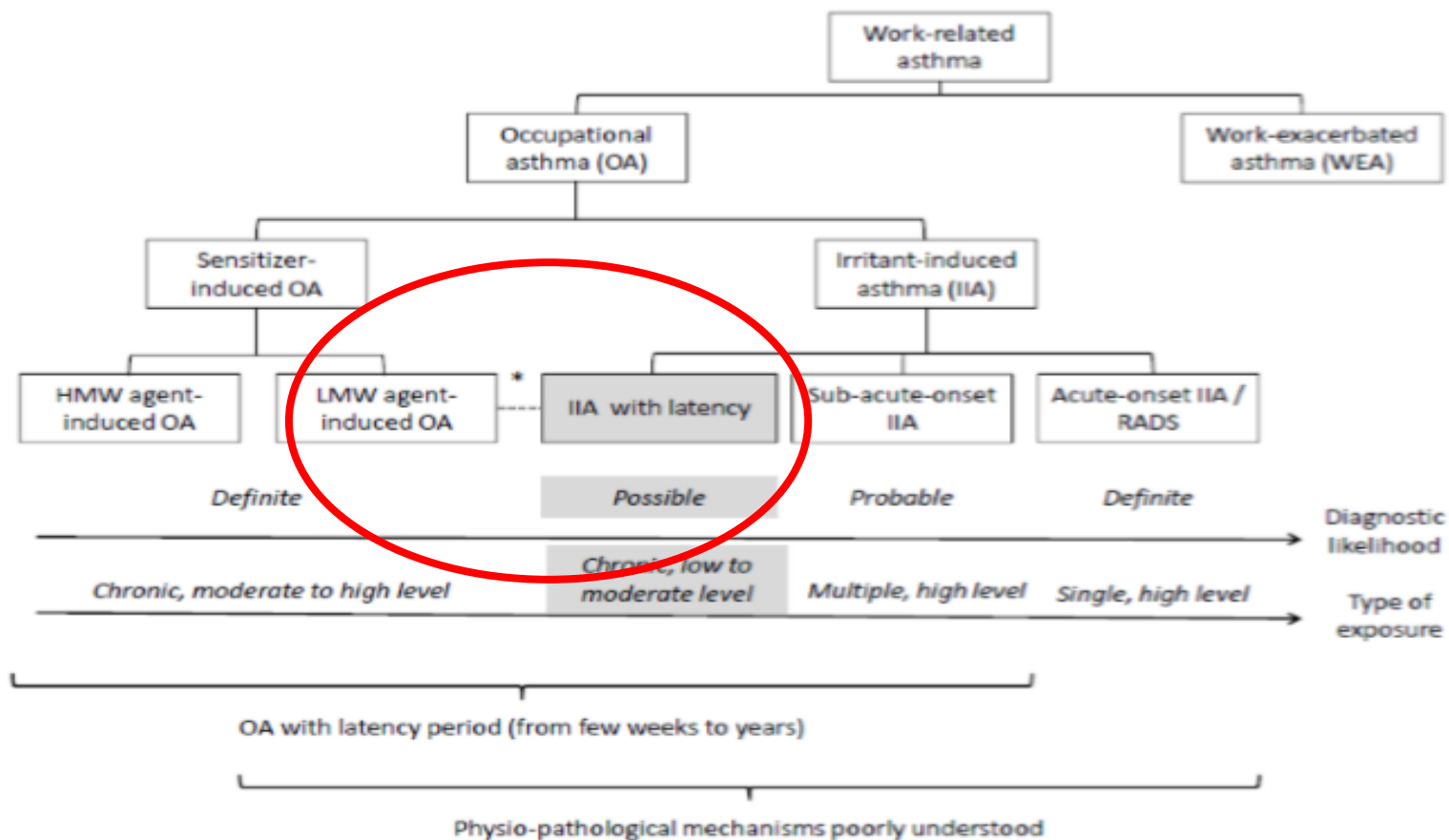


Figure 1. Description of various forms of work-related Asthma.



* For many agents (chemicals), it is difficult to distinguish possible IIA with latency from LMW agent-induced asthma

IIA: Irritant Induced Asthma; HMW: High Molecular Weight; LMW: Low Molecular Weight; OA:

**Do chronic workplace irritant exposures cause asthma?
O.Dumas, 2016**

LINEE GUIDA PER LA FORMAZIONE CONTINUA E L'ACCREDITAMENTO DEL MEDICO DEL LAVORO

Series Editors: P. Apostoli, PA Bertazzi, L. Isolani, M. Imbriani, G. Abbritti.

2009

Società Italiana di Medicina del Lavoro e Igiene Industriale

LINEE GUIDA

per la sorveglianza sanitaria di lavoratori esposti ad irritanti e tossici per l'apparato respiratorio

P. Maestrelli (*coordinatore*)

P. Boschetto, P. Carta, M. Corradi, R. De Zotti, L. Di Lorenzo, M. Ferrari, G. Guarnieri, M. Imbriani, A. Innocenti, C. Mapp, N. Murgia, G. Muzi, L. Patrini, A. Quercia, L. Riboldi, C. Romano, L. Soleo

Tabella 2: Agenti associati con asma da irritanti (87-90)

AGENTE	TIPO DI STUDIO	EVIDENZE*
Isocianati	Case reports + sperimentale	A, S, IB, P
Ossido di etilene	Case report	A, S, IB, P
Dietilamminoetano	Case report	A, S
Fumi di saldatura	Case report	A, S, IB, P
Ipoclorito di sodio	Case report	A, S, IB
Acido cloridico	Case reports	A, S, IB
Acido acetico	Case report	A, S, IB
Cloro	Case reports + epidemiologico	A, S, IB, P
Diossido di zolfo	Case reports	A, S, IB, P
Ammoniaca	Case reports	A, S, IB, P
Solfuro di idrogeno	Case report	A, S, IB
Bromo e acido bromico	Case reports	A, S, IB
Acidi (vari)	Case reports	A, S, IB, P
Ossido di calcio	Case report	A, S, IB
Ossido di etilene	Case report	A, S, IB, P
Cloropicrina	Sperimentale	P



Table 1. Chemicals in cleaning products commonly involved in work-related respiratory symptoms

Sensitizers

- Amine compounds (eg, monoethanolamine)
- Disinfectants (eg, aldehydes)
- Quaternary ammonium compounds (eg, benzalkonium chloride)
- Scents containing terpenes (eg, pinene, d-limonene), eugenol
- Isothiazolinones, formaldehyde (preservatives)
- Others: natural rubber latex

Irritants

- Chlorine (bleach)
- Ammonia
- Hydrochloric acid
- Monochloramine
- Mixing bleach and acid or ammonia
- Sodium hydroxide (caustic soda)
- Quaternary ammonium compounds
- Monoethanolamine

S. Quirce et al, J Investig Allergol Clin Immunol 2010;20:542-50

Table 2 Examples of exposures causing acute-onset irritant-induced asthma

Exposure	Examples
Gases	Chlorine (e.g. released by mixing sodium hypochlorite with acids), chloramines (released by mixing sodium hypochlorite with ammonia) sulfur dioxide, nitrogen oxides, dimethyl sulfate
Acids	Acetic, hydrochloric, hydrofluoric, and hydrobromic acids
Alkali	Ammonia, calcium oxide (lime), hydrazine
Biocides	Formalin, ethylene oxide, fumigating agents, insecticides (sodium methyldithiocarbamate, dichlorvos)
Halogenated derivatives	Bromochlorodifluoromethane (fire extinguisher), trifluoromethane, chlorofluorocarbons (CFC) (thermal degradation products of freons), orthochlorobenzylidene malonitrile (tear gas), uranium hexafluoride, hydrogen and carbonyl fluoride
Solvents	Perchloroethylene
Fumes	Diesel exhaust, paint fumes, urea fumes, fire smoke, fumes of iodine and aluminum iodide, diethylaminoethanol (corrosion inhibitor)
Sprays	Various paints (not specified), floor sealant (aromatic hydrocarbons)
Dusts	World Trade Centre alkaline dust, calcium oxide (lime)
Potential sensitizers	Isocyanates, phthalic anhydride

Vandenplas, EAACI position paper 2014

DIAGNOSI

- ✓ Anamnesi → questionari (ECRHS, CECA, Siml)
- ✓ Spirometria/ Test di broncodilatazione/
Iperreattività bronchiale
- ✓ Test di provocazione bronchiale specifico
(esposizione all'agente irritante in Centri
specializzati)
- ✓ Monitoraggio del PEF al lavoro e fuori dal lavoro
(fenomeno arresto-ripresa)



DIAGNOSI



Diagnosi differenziale con:

- **VCD (disfunzione delle corde vocali)**
- **Sindrome da iperventilazione**
- **MCS (multiple chemical sensitivity syndrome)**



Non-IgE-mediated and irritant-induced work-related rhinitis

Andrea Siracusa^a, Ilenia Folletti^a, and Gianna Moscato^b

Purpose of review

Recently there has been growing interest in non-IgE-mediated and irritant-induced occupational rhinitis due to old and new low-molecular-weight and irritant agents. The purpose of this review is to summarize the scientific evidence on agents and work activities responsible for non-IgE-mediated and irritant-induced occupational rhinitis and work-exacerbated rhinitis published in 2011 and 2012.

Recent findings

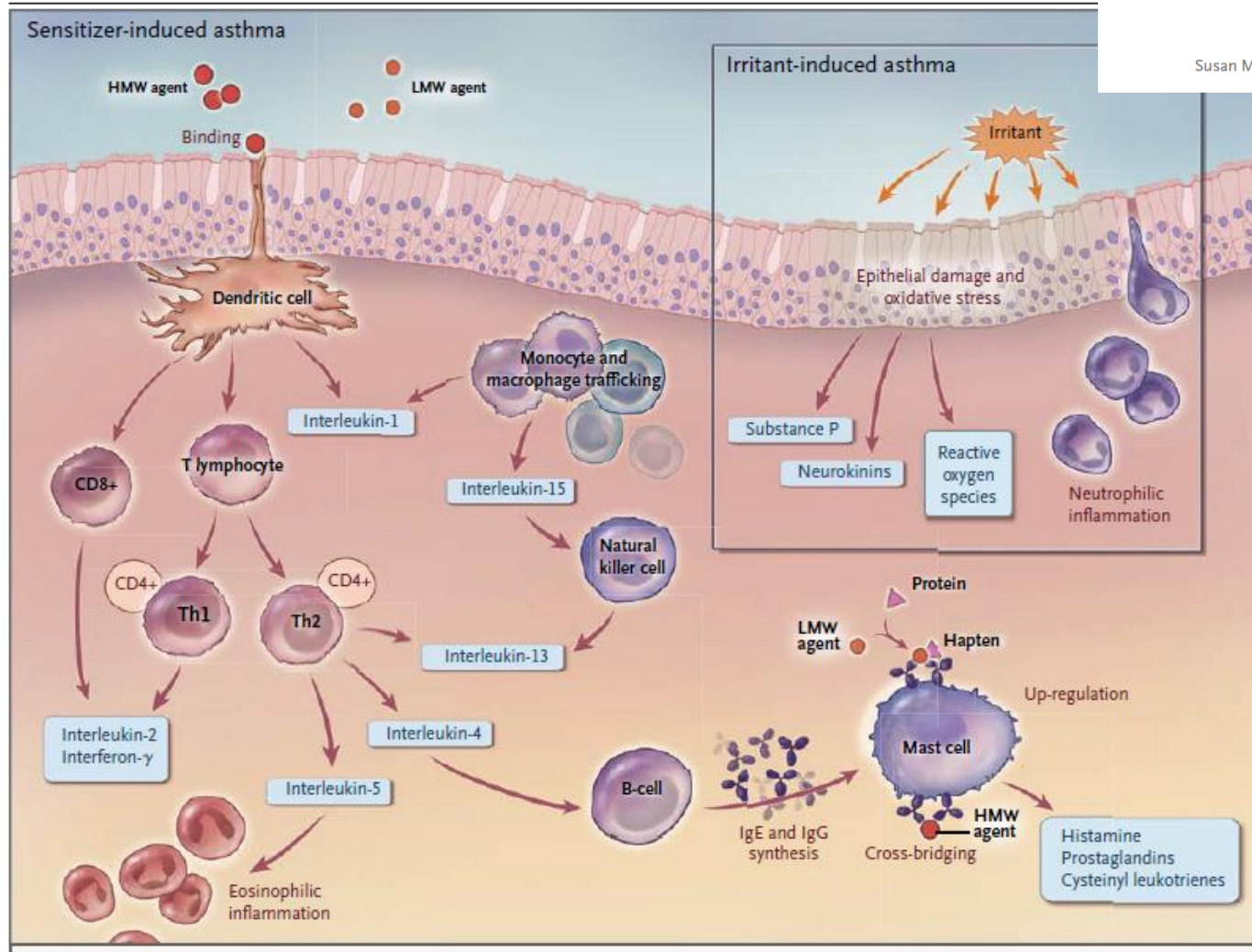
Several epidemiological, surveillance and experimental studies, case reports and reviews showed that workers exposed to drugs, wood dust, chemicals, metals and biocides are at high risk of non-IgE-mediated and irritant-induced occupational rhinitis; among activities at risk are healthcare, antibiotic manufacturing and cleaning workers. Work-exacerbated rhinitis has not been specifically studied, but it is reasonable to expect that it is frequently associated with work-exacerbated asthma. Recently, work-related anosmia/microsmia, nasal polyps and sinusitis have also been described. Reducing or eliminating workplace exposure to the specific agent has been confirmed to be effective in preventing symptoms of nonallergic occupational rhinitis.

Summary

In consideration of the relevance of non-IgE-mediated and irritant-induced work-related rhinitis, physicians should recognize work-related rhinitis symptoms due to old and new low-molecular-weight and irritant agents. The mechanisms of non-IgE-mediated and irritant-induced occupational rhinitis remain largely unclear and need to be studied further. Substitution of responsible agents, reduction or elimination of exposure at the workplace should be enforced as effective measures.

Occupational Asthma

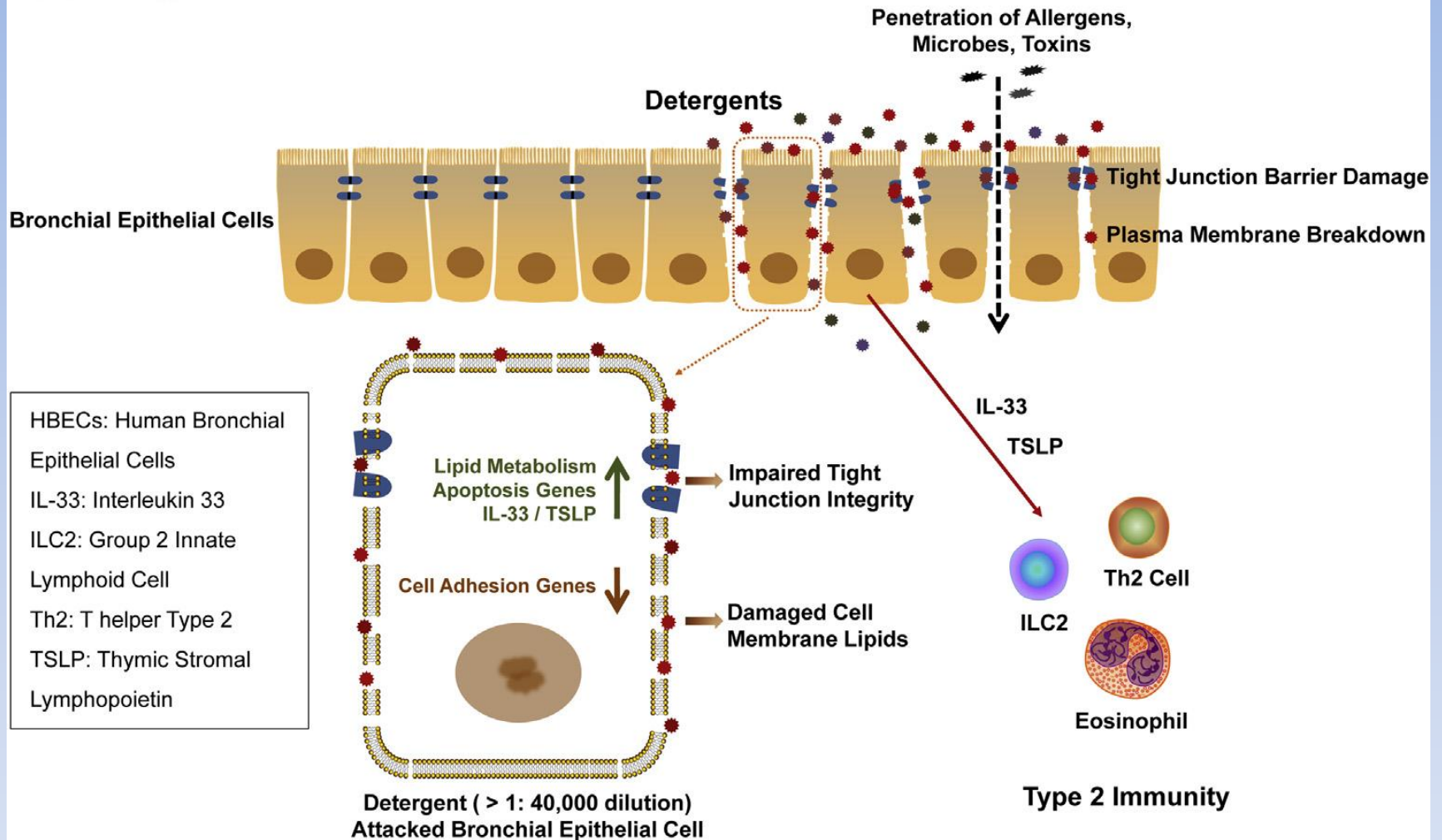
Susan M. Tarlo, M.B., B.S., and Catherine Lemiere, M.D.



Danno epiteliale
Stress ossidativo
Rilascio di:
-Sostanza P
-Neurochine
-Interleukine es IL1 e 15
-Infiammazione
neutrofila



Detergents Directly Disrupt Tight Junction Barrier in HBECs



Environmental and occupational disease

Laundry detergents and detergent residue after rinsing directly disrupt tight junction barrier integrity in human bronchial epithelial cells



Wang, 2019

ORIGINAL RESEARCH

Formaldehyde Induces Rho-Associated Kinase Activity to Evoke Airway Hyperresponsiveness

Joseph Jude¹, Cynthia Koziol-White¹, Jacqueline Scala¹, Edwin Yoo¹, William Jester¹, Christopher Maute², Pamela Dalton², and Reynold Panettieri, Jr.¹

¹Rutgers Institute for Translational Medicine & Science, Child Health Institute of New Jersey, Rutgers, The State University of New Jersey, New Brunswick, New Jersey; and ²Monell Chemical Senses Center, Philadelphia, Pennsylvania

Abstract

Formaldehyde, a common indoor air pollutant, exacerbates asthma and synergizes with allergen to induce airway hyperresponsiveness (AHR) in mediating formaldehyde-induced

of Nrf-2 induction little effect on airway hyperresponsiveness in cocultured H1hESC cells. We posit that formaldehyde mediates



This information is current as of August 9, 2019.

CysLT₁ Receptor Is Protective against Oxidative Stress in a Model of Irritant-Induced Asthma

Toby McGovern, Madison Goldberger, Michael Chen, Benoit Allard, Yoichiro Hamamoto, Yoshihide Kanaoka, K. Frank Austen, William S. Powell and James G. Martin

J Immunol 2016; 197:266-277; Prepublished online 25 May 2016;
doi: 10.4049/jimmunol.1501084
<http://www.jimmunol.org/content/197/1/266>



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Environment International

journal homepage: www.elsevier.com/locate/envint



Genome-wide interaction study of gene-by-occupational exposures on respiratory symptoms

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Genes Interacting with Occupational Exposures to Low Molecular Weight Agents and Irritants on Adult-Onset Asthma in Three European Studies

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Ivan Curjuric,^{11,12} Marie-Hélène Dizier,^{9,10} Orianne Dumas,^{1,8} Juan R. Gonzalez,^{6,7} Medea Imboden,^{11,12}
Amar J. Mehta,^{11,12,13} Pascale Tubert-Bitter,^{3,4,5} Jan-Paul Zock,^{6,7,14} Deborah Jarvis,^{15,16}
Nicole M. Probst-Hensch,^{11,12} Florence Demenais,^{9,10†} and Rachel Nadif^{1,8†}

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acting with exposure do not belong to protein-coding regions; rather, they are more likely to have a regulatory function, as indicated by the functional annotations of a few of these SNPs. *RELA* encodes the RelA protein, which is complexed with NFKB1, the most abundant form of NF- κ B. *PRKD1* encodes a serine/threonine kinase called PKD1, which activates NF- κ B in response to oxidative stress conditions (Sundram et al. 2011; Storz 2007). Exposure to a photochemically altered

Conclusions

In conclusion, the present study identified new and promising candidate genes interacting with occupational exposures to LMW agents or irritants in current adult-onset asthma. More generally, this study highlights the interest in performing G \times E interaction analyses to identify new genes and mechanisms of asthma occurrence related to specific environmental exposures.

1. Caso clinico



- Donna di **44 anni, atopica**, non fumatrice, affetta da rinocongintivite e asma allergici, in remissione dall'età adolescenziale
- **Da 15 anni biologa** nel laboratorio chimico e microbiologico di un impianto di trasformazione delle uova per l'industria alimentare
- **inalazione accidentale di fumi di acqua regia** → miscela di acido nitrico e cloridrico utilizzato per la pulizia dell'impianto **$\text{HNO}_3 + \text{HCl}$**
- **mal di gola e febbre per 2 giorni e tosse con dispnea e respiro sibilante accompagnata a senso di costrizione toracica**
- Da allora numerose esacerbazioni dei sintomi d'asma in seguito a infezioni virali, esercizio fisico, basse temperature, umidità e odori forti.

- A 3 anni dall'evento i test di funzionalità respiratoria hanno mostrato una **lieve ostruzione bronchiale**, che era parzialmente reversibile ed una media iperreattività bronchiale
- Il monitoraggio del PEF ha documentato una variabilità superiore al 20%
- Il trattamento con ICS-LABA ha migliorato i sintomi dell'asma
- *I test di funzionalità respiratoria al momento dell'incidente acuto per inalazione non erano disponibili.*
- La RADS è stata diagnosticata sulla base di sintomi respiratori persistenti e l'ostruzione delle vie aeree reversibile 3 anni dopo l'inalazione accidentale

Table 2 Examples of exposures causing acute-onset irritant-induced asthma

Exposure	Examples
Gases	Chlorine (e.g. released by mixing sodium hypochlorite with acids), chloramines (released by mixing sodium hypochlorite with ammonia) sulfur dioxide, nitrogen oxides, dimethyl sulfate
Acids	Acetic, hydrochloric, hydrofluoric, and hydrobromic acids
Alkali	Ammonia, calcium oxide (lime), hydrazine
Biocides	Formalin, ethylene oxide, fumigating agents, insecticides (sodium methyldithiocarbamate, dichlorvos)
Halogenated derivatives	Bromochlorodifluoromethane (fire extinguisher), trifluoromethane, chlorofluorocarbons (CFC) (thermal degradation products of freons), orthochlorobenzylidene malonitrile (tear gas), uranium hexafluoride, hydrogen and carbonyl fluoride
Solvents	Perchloroethylene
Fumes	Diesel exhaust, paint fumes, urea fumes, fire smoke, fumes of iodine and aluminum iodide, diethylaminoethanol (corrosion inhibitor)
Sprays	Various paints (not specified), floor sealant (aromatic hydrocarbons)
Dusts	World Trade Centre alkaline dust, calcium oxide (lime)
Potential sensitizers	Isocyanates, phthalic anhydride

2. Caso clinico, asma insorta in età adulta

- Donna di **50 anni**, obesità di I grado, non fumatrice, ipertensione arteriosa in terapia, **lavora da 7 anni addetta all'allevamento di suini**, esegue tutte le mansioni in particolare la pulizia delle griglie del pavimento della stalla con **ipoclorito di sodio e acqua**
- Non atopia, non eosinofilia
- Dopo 4 anni di esposizione lavorativa ha iniziato ad avere irritazione delle prime vie aeree, senso di oppressione toracica e tosse stizzosa durante e dopo la pulizia delle griglie
- Diagnosi di asma bronchiale con test di broncodilatazione positivo e media iperreattività bronchiale
- Miglioramento dei sintomi dopo terapia ICS-LABA , ha continuato il lavoro evitando le pulizie
- Attualmente non svolge più il lavoro e l'asma è meglio controllata



Swine confinement building

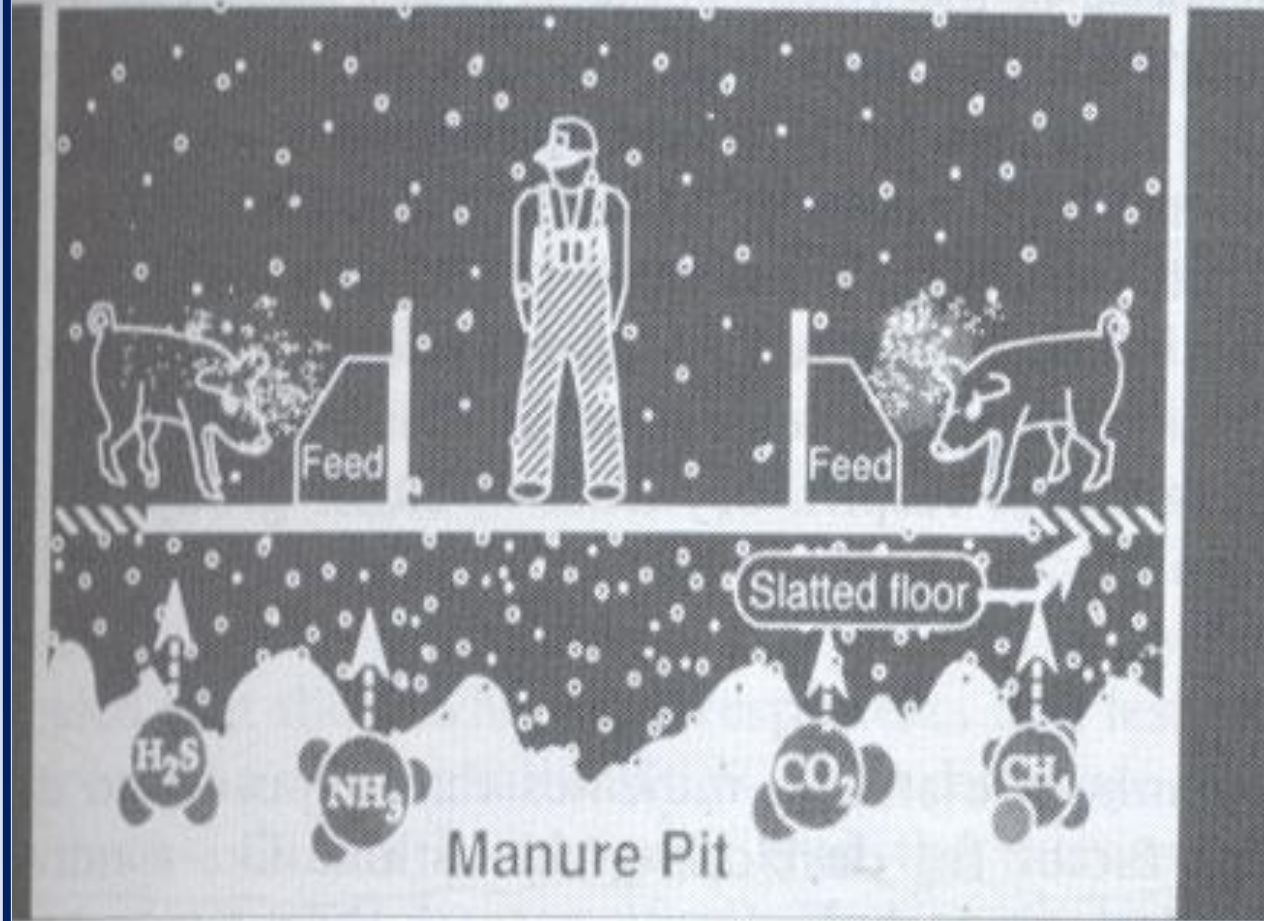


Table 6 Examples of work exposures involved in possible irritant-induced asthma

High-risk occupation	Irritants	Irritants with a sensitizing potential
Cleaners	Bleach, ammonia, cleaning/degreasing sprays	Disinfectants (glutaraldehyde, QACs, chloramine-T, isothiazolinone), ethanolamines, enzymes, surfactants
Aluminum smelting	Fluorides, SO ₂	Aluminum
Swine and dairy production	Aerosols from endotoxins and organic dusts, manure gases	QACs, animal allergens
Dark-room environment	SO ₂ , acetic acid	Glutaraldehyde, formaldehyde
Sulfurization	SO ₂	None identified
Welding	Nitrogen oxides, fluorides, ozone	Chromium, nickel
Pesticides	Organophosphates, methylcarbamates, ...	Pyrethroids, phytophagous and predatory mites
Wood industry	Wood dust	Wood dust (e.g. plicatic acid)

QACs, quaternary ammonium compounds.

Tarlo SM et al. *Diagnosis and management of work-related asthma: American College Of Chest Physicians Consensus Statement. Chest 2008;134:1S–41S.*

PREVENZIONE (primaria)

- ✓ La prevenzione deve includere misure igieniche occupazionali che garantiscano la sicurezza dei lavoratori negli ambienti in cui c'è il rischio di esposizione accidentale ad irritanti (sistemi di allarme)
- ✓ Misure generali includono il contenimento dell'inquinante, una buona ventilazione ambientale, la formazione ed informazione del lavoratore in merito alle principali pratiche di sicurezza e l'uso di dispositivi di protezione delle vie aeree
- ✓ Screening pre-assuntivo per i soggetti con asma severo per evitare i lavori con esposizione ad agenti irritanti sembra plausibile MA gli effetti NON SONO DOCUMENTATI

PREVENZIONE (secondaria)

- ✓ La sorveglianza sanitaria non ha rilevanza per l'esposizione ACUTA ad agenti irritanti ma può avere un ruolo per la diagnosi precoce nei casi di asma sub-acuta/cronica

PREVENZIONE (terziaria)

Management dell'asma

- ✓ Terapia dell'asma
- ✓ Allontanamento del soggetto dall'agente irritante non ha evidenze scientifiche nell'asma da irritanti, la riduzione dell'esposizione può prevenire riacutizzazioni



HHS Public Access

Author manuscript

Int J Tuberc Lung Dis. Author manuscript; available in PMC 2015 September 23.

Published in final edited form as:

Int J Tuberc Lung Dis. 2015 February ; 19(2): 244–250. doi:10.5588/ijtld.14.0132.

Occupational exposures associated with severe exacerbation of asthma

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Allergy Asthma Immunol Res. 2019 Mar;11(2):188-200
<https://doi.org/10.4168/aa.2019.11.2.188>
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research **AAIR**^{*}

Review



Update on the Management of Occupational Asthma and Work-Exacerbated Asthma

Ambrose Lau, Susan M. Tarlo

Despite the lack of sensitization, patients with irritant-induced asthma will likely continue to have evidence of asthma long-term and may require ongoing therapy.⁵⁷ Due to the nature of the injury, patients may have comorbid conditions that will complicate their asthma care, including depression, post-traumatic stress disorder, occupational rhinitis, multiple chemical sensitivity syndrome and vocal cord dysfunction.



Article

Air Pollution/Irritants, Asthma Control, and Health-Related Quality of Life among 9/11-Exposed Individuals with Asthma

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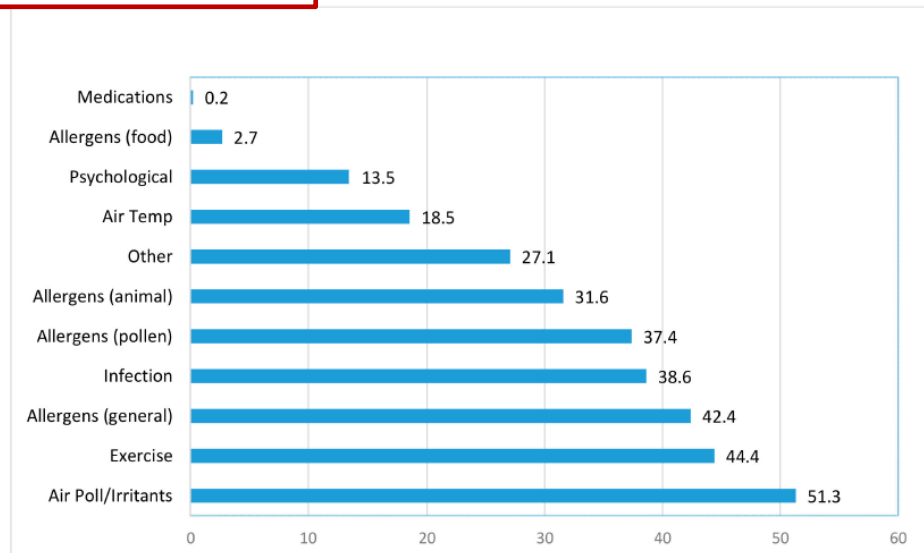


Figure 1. Percentage of each self-reported asthma trigger among World Trade Center Health Registry enrollees with asthma (not mutually exclusive).

Asthma control status by sociodemographic characteristics, comorbid conditions, reporting air pollution/irritants as an asthma trigger, and WTC dust exposure are shown in Table 1. The overall prevalence of poorly-controlled and very poorly-controlled asthma were 27.1% and 32.2%, respectively. We also observed an increase in prevalence of very poorly-controlled asthma among those with self-reported air pollution/irritants trigger (39.8%), depression (55.8%), and probable PTSD (58.1%).

CONCLUSIONI

- ✓ Le conoscenze riguardo all'asma indotta da agenti irritanti sono in parte limitate anche per la mancanza di **studi longitudinali** e per la mancanza di studi volti a **valutare/misurare l'esposizione**
- ✓ Molte attività lavorative sono caratterizzate dalla possibile esposizione ad agenti inalanti irritanti
- ✓ La **sorveglianza sanitaria** dei lavoratori esposti ed il monitoraggio ambientale possono essere strumenti utili a implementare le conoscenze in tale ambito e mettere in atto efficaci misure preventive
- ✓ I pazienti/lavoratori che manifestano asma in età adulta devono essere sottoposti ad un'attenta **valutazione anamnestica lavorativa** ed extra-lavorativa per valutare l'esposizione a sostanze irritanti per le vie aeree



Grazie