

# Irritanti e tossici respiratori emergenti: il problema del cloro e dei suoi derivati

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Università degli Studi di Parma

340

THE BULLETIN

## PULMONARY IRRITANTS \*

ROBERT A. KEHOE

Research Professor of Physiology  
College of Medicine, University of Cincinnati

### CLASSIFICATION OF PULMONARY IRRITANTS

**P**ULMONARY irritant or injurant substances comprise a group of compounds that exist as gases, or as liquids that have a sufficiently high vapor pressure under ordinary conditions to give rise to injurious concentrations in respired air.

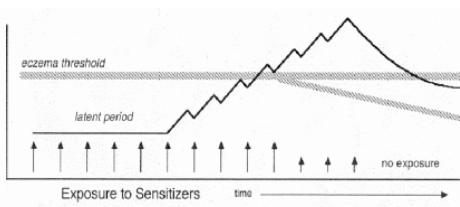
*Bull N Y Acad Med. 1943 May; 19(5): 340-355.*

## Effetti respiratori degli irritanti aerodispersi

- Possono aggravare una pre-esistente asma
- Possono causare, in caso di inalazione massiva, l'asma indotta da irritanti (RADS)
- Possono causare asma occupazionale
- **Favoriscono la sensibilizzazione allergica?**
- **Favoriscono un cronico danno polmonare?**

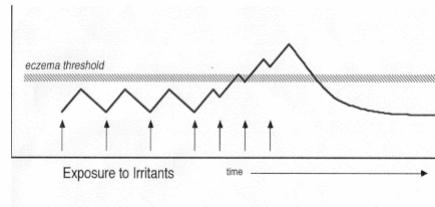
## Allergene vs. irritante

L'asma può essere allergica ?



Trascorre un lungo periodo (da settimane ad anni) di contatto senza che si manifesti la reazione (**latenza**) e quindi compare un evento con pattern in 'crescendo' si ripresenta per esposizioni di sempre minore intensità

L'asma può essere irritativa ?



Si manifesta subito dopo il contatto (**senza latenza**); non bene identificabile un pattern in 'crescendo' Recidiva con la stessa intensità e per pari durata di esposizione

### Elenco di alcune sostanze classificate come irritanti respiratori dell'UE e considerate URT irr dall'ACGIH, nel 2008

Aldeide Propionica	Dicloruro di cromile	Fosgene
Allilglicil etere	Dicloruro di tienile	2-furaldeide
Ammoniaca, anidra	Diceromato di ammonio	Glicidolo
Anidride acetica	Diceromato di potassio	Glutaraldeide
Anidride italica	Diceromato di sodio	Iscianato di metile
Benomil	Diceromato di sodio, diidrato	Isoforone
Benzotrichloruro	Dietilamina	Isopropilammmina
N-butanolo	2-dietilaminoetanolo	Metacrilato di metile
Butan-2-olo	Diisocianato di esametilene	Metilamil alcool
Butilamina	Diisopropilamina	Metilbromuro
Calciocianamide	2,6-dimetil-epant-4-one; diisobutilchetone	Metilisobutilchetone
E-Caprolattame	Dimetilamina	Alfa-metilstirene
2-Cianoacrilato di etile	Dimetilcarbamoil cloruro	Monometilammmina
2-Cianoacrilato di metile	Diossido di azoto	Ossido di propilene
Cloro	Esametilendiamina	Pentaclorofenolo
Cloroacetaledeide	Etile silicato	Pentacloruro di antimonio
Cloroprene	Ferbam	Pantan-3-one; dietilchetone
Cloruro di allile	Formaldeide	Perossido di idrogeno
Cloruro di benzile	Formiato di etile	Rotenone
Cloruro di zinco	Formiato di metile	Subtilisina
Cromato di potassio		Tetracloruro di stagno
Cromato di sodio		
Crotonaldeide		
Cumene		

*Linee Guida SIMLII 2009*

### La clorazione è il sistema più utilizzato per la disinfezione delle acque

#### Cloro

- cloro
- ipoclorito di sodio e di calcio
- cloro-isocianurati



↓  
L' ipoclorito ( $\text{ClO}^-$ ) corrisponde al **Cloro attivo libero** ed è il vero agente disinfettante

## Effetti sulla salute indotti dalla inalazione di prodotti clorurati

### Effetti acuti:

- irritazione di cute e mucose e sintomi alle vie aeree superiori e inferiori

### Effetti cronici:

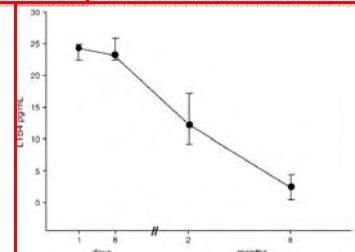
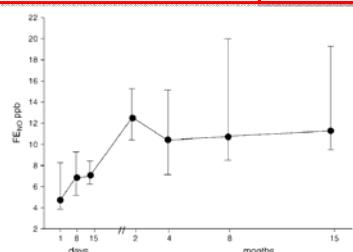
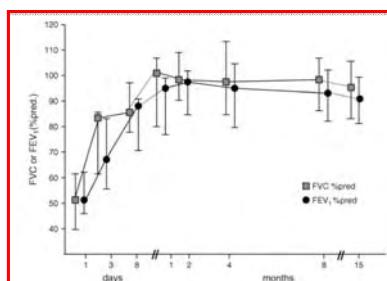
- Alterazioni della funzione respiratoria?
- Effetto pro-sensibilizzante?

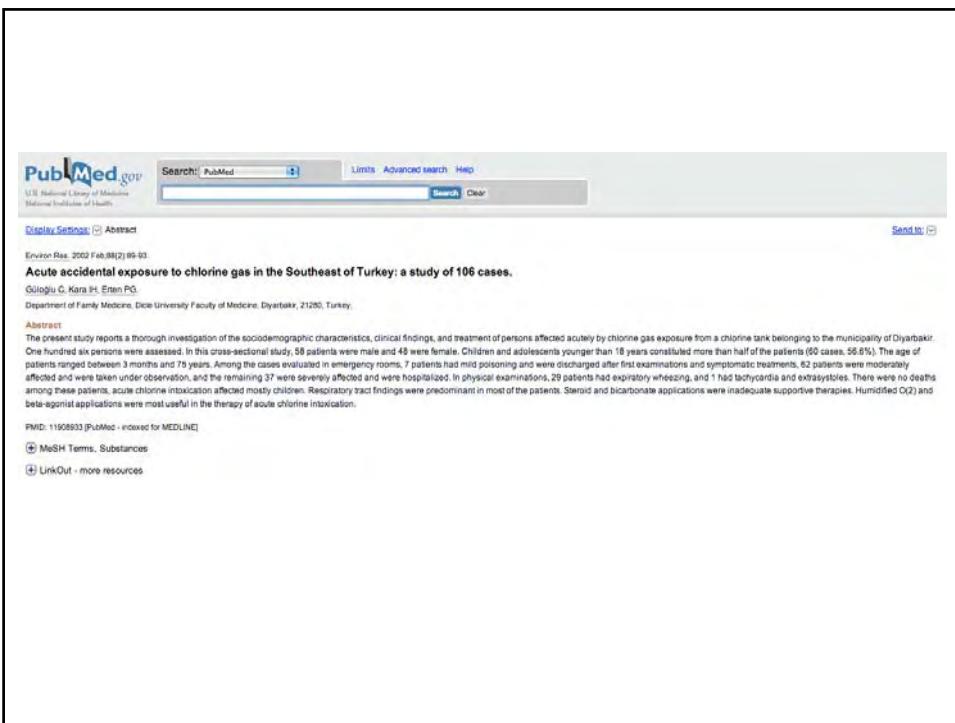
### Longitudinal Monitoring of Lung Injury in Children after Acute Chlorine Exposure in a Swimming Pool

AMERICAN JOURNAL OF  
ATS Respiratory and  
Critical Care Medicine®

Gea Bonetto, Massimo Corradi, Silvia Carraro, Stefania Zanconato, Rossella Alinovi, Giuseppina Folesani,  
Liliana Da Dalt, Antonio Mutti, and Eugenio Baraldi

Department of Pediatrics, University of Padua, Padua; and Laboratory of Industrial Toxicology, Department of Clinical Medicine, Nephrology,  
and Health Sciences and National Institute of Occupational Safety and Prevention Research Center, University of Parma, Parma, Italy





## Effetti sulla salute indotti dalla inalazione di prodotti clorurati

### Effetti acuti:

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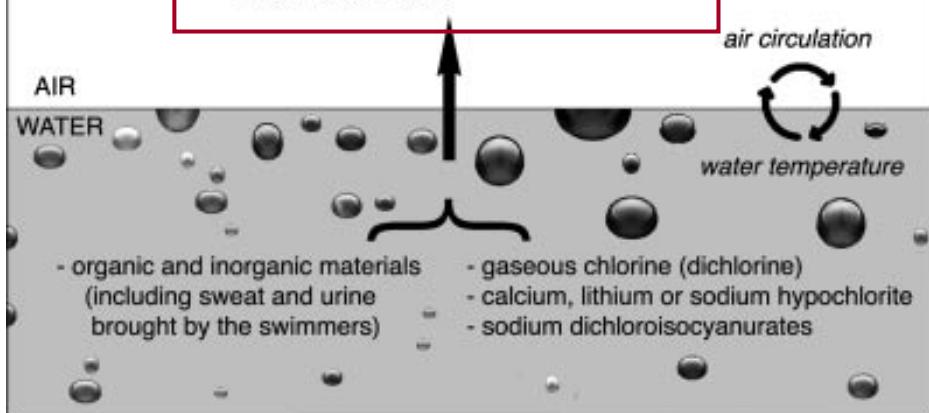
- Alterazioni della funzione respiratoria?
- Effetto pro-sensibilizzante?

**Durante il nuoto si respira una grande quantità  
di aria depositata sulla superficie dell'acqua,  
ma anche microaspirazioni di acqua**



**Disinfection by-products (DBP)**

- chloramines
- trihalomethanes
- haloacetonitriles
- haloacetic acid
- chloropicrin



NCBI Resources How To

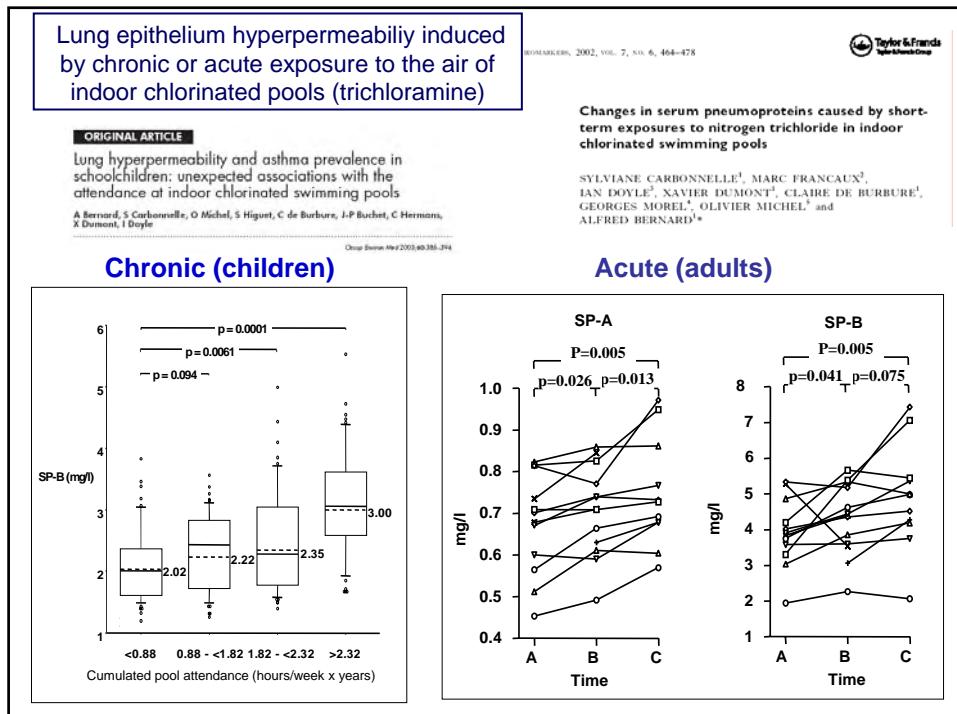
**PubMed.gov**  
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National Institutes of Health

Search: PubMed RSS Save search Limits Advanced search Help  
swimming pool and asthma Search Clear

Display Settings: Summary, 20 per page, Sorted by Recently Added

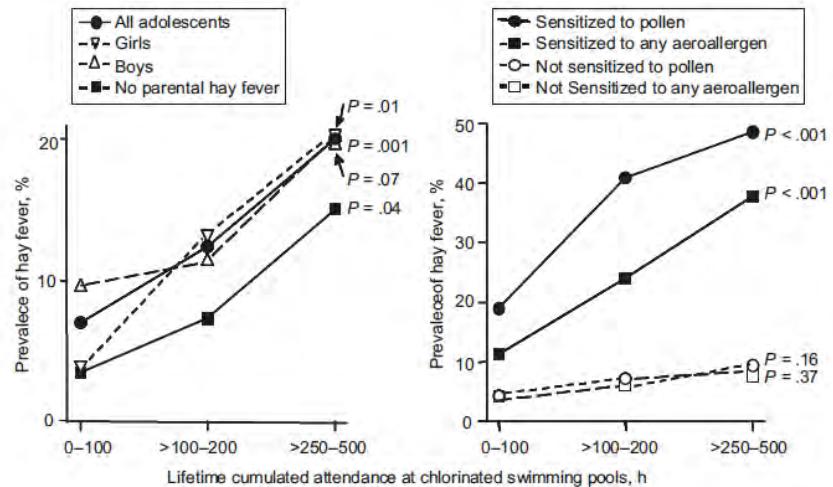
**Results: 1 to 20 of 56**

- [Infant swimming in chlorinated pools and the risks of bronchiolitis, asthma and allergy.](#)
- 1. Voisin C, Sardella A, Marcucci F, Bernard A. Eur Respir J. 2010 Jan 14. [Epub ahead of print] PMID: 20075053 [PubMed - as supplied by publisher] [Related citations](#)
- [Exhaled nitric oxide and airway hyperresponsiveness in workers: a preliminary study in lifeguards.](#)
- 2. Demange V, Bohadana A, Massin N, Wild P. BMC Pulm Med. 2009 Dec 31;9:53. PMID: 20043846 [PubMed - indexed for MEDLINE] [Free PMC Article](#) [Free text](#) [Related citations](#)
- [Effects of chlorine and exercise on the unified airway in adolescent elite Scottish swimmers.](#)
- 3. Clearie KL, Vaidyanathan S, Williamson PA, Goudie A, Short P, Schembri S, Lipworth BJ. Allergy. 2010 Feb;65(2):269-73. Epub 2009 Sep 30. PMID: 19793061 [PubMed - indexed for MEDLINE] [Related citations](#)
- [Impact of chlorinated swimming pool attendance on the respiratory health of adolescents.](#)
- 4. Bernard A, Nickmilder M, Voisin C, Sardella A. Pediatrics. 2009 Oct;124(4):1110-8. Epub 2009 Sep 14. PMID: 19752078 [PubMed - indexed for MEDLINE] [Related citations](#)
- [Effect of swimming on peak expiratory flow rate of atopic children.](#)
- 5. Bemanian MH, Shirkhoda S, Nakjavani M, Mozafari H. Iran J Allergy Asthma Immunol. 2009 Jun;8(2):121-3. PMID: 19871943 [PubMed - indexed for MEDLINE] [Related citations](#)
- [Widening of the pool of factors: studies needed to assess asthma-swimming link.](#)
- 6. Spivey A. Environ Health Perspect. 2009 Apr;117(4):A162. No abstract available. PMID: 19440481 [PubMed - indexed for MEDLINE] [Free PMC Article](#) [Free text](#) [Related citations](#)



## Impact of Chlorinated Swimming Pool Attendance on the Respiratory Health of Adolescents

Alfred Bernard, Marc Nickmilder, Catherine Voisin and Antonia Sardella  
*Pediatrics* 2009;124:1110-1118; originally published online Sep 14, 2009;  
 DOI: 10.1542/peds.2009-0032



### Chlorine/atopy interaction in the development of childhood asthma: adjuvant effect of chlorination products

#### Environews | Science Selections

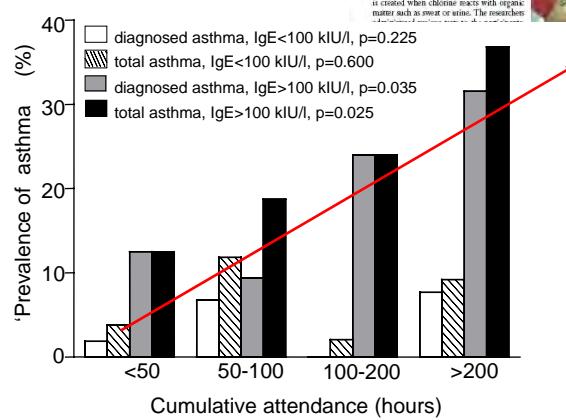
##### Swimming in Allergens?

**Pool Use and Asthma**  
 Atopic asthma (inflammation of the airways caused by exposure to airborne allergens) has become increasingly prevalent since the 1960s and is now the most common chronic childhood disease in the United States and many other industrialized countries. The cause of the rise is unclear, though many hypotheses have been put forth. Now, however, a new finding that further supports one proposed reason—increased use of indoor chlorinated swimming pools by children (*EHP* 114:1567–1573; Bernad et al.).

just after family history of asthma or hay fever is tendency toward developing IgE-mediated allergic diseases. Time spent at pools was associated with asthma only in children with elevated serum dose-related and most strongly linked to pool attendance. At age of about 7 years, suggests the authors, children, especially boys with atopic traits, are at risk of childhood atopic asthma.

The researchers suggest that chlorine-trichloramine disrupt barriers of the respiratory tract, similar to findings by earlier findings for children who used a chlorine-based bleach. Bleach damage to the lungs occurs after a little over 1 hour.

The findings suggest that pools, especially chlorinated, may contribute to the development of childhood atopic asthma.



Damage to the lung epithelium associated with baby swimming practice (before 2 years)



**Table 1** Children characteristics and serum levels of IgE, CC16 and SP-D

	Swimming baby (n = 43)	Other children (n = 298)	P Value
Age, (mean, SD), y*	11.5 (0.6)	11.5 (0.6)	.98
Boys, N°, (%)†	22 (51.1)	150 (50.3)	.92
Caucasian, N°, (%)†	35 (81.4)	228 (76.5)	.48
Mother and/or father with asthma, N°, (%)†	6 (14.0)	58 (19.5)	.39
Aeroallergen-specific IgE, N°, (%)†	13 (30.2)	95 (31.9)	.83
Total IgE, (median, IQR), kU/l‡	54.7 (24.6-162)	55.8 (21.9-175)	.96
CC16, (mean, SD), µg/l*§	8.0 (3.3)	10.4 (4.2)	.01
SP-D, (mean, SD), µg/l*§	113 (42)	100 (45)	.08
CC16/SP-D ratio, (median, IQR)‡ §	0.07 (0.05-0.12)	0.10 (0.07-0.16)	.003

Abbreviations: CC16, Clara cell protein, SP-D, surfactant-associated protein D, IQR, interquartile range

\* By two-sided unpaired *t* test

† By  $\chi^2$  test

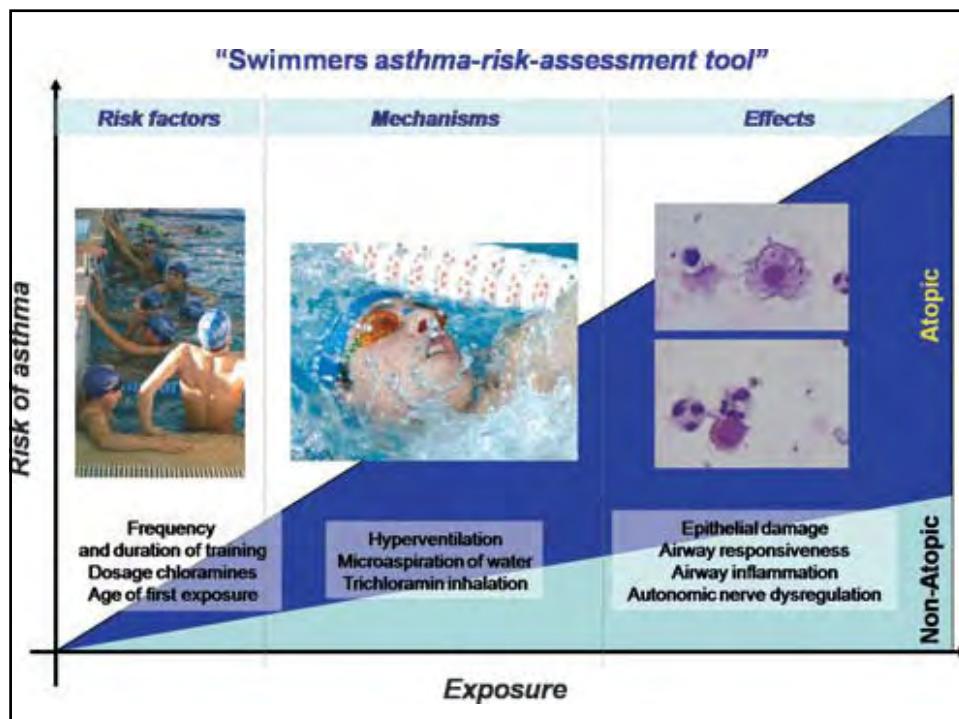
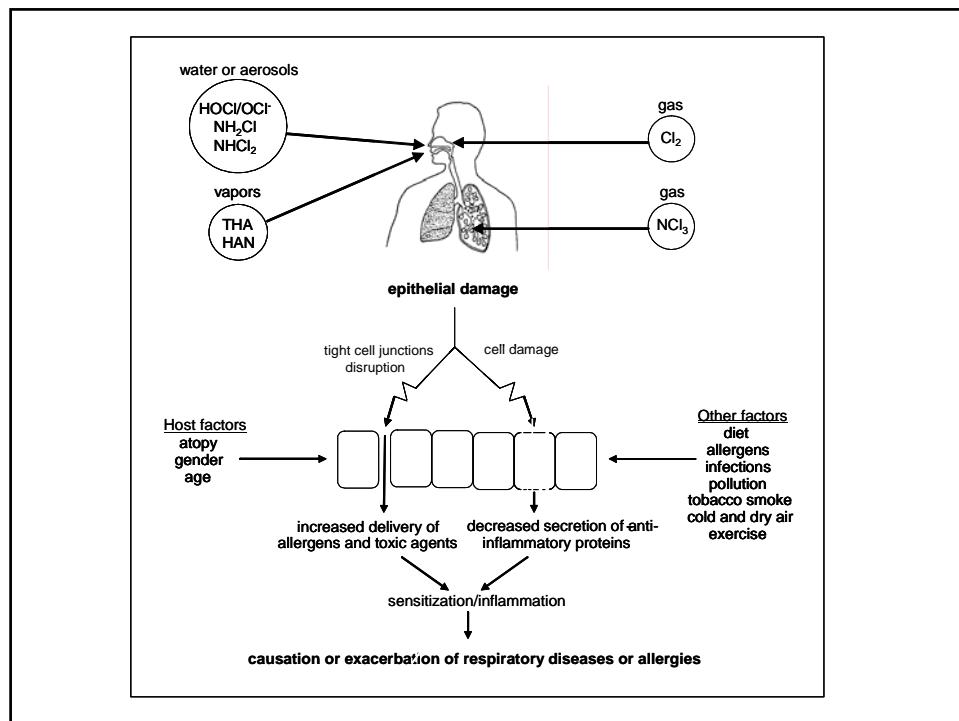
‡ By two-sided Mann-Whitney *U* test

§ Statistically significant after application of the Benferroni's correction to the multiple comparisons of the lung epithelium markers (critical *P* Value: 0.05/3).

Bernard *et al.* Pediatrics (2007)

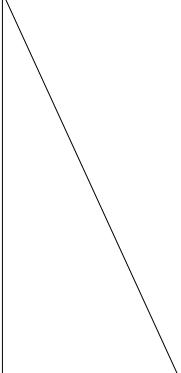
## Frequenza di piscine e rischio di asma?

- *Ipotizzato un effetto avverso sulla funzionalità di specifiche cellule polmonari in bambini che frequentano regolarmente piscine coperte: alterata produzione di una proteina antinfiammatoria CC16*
- *Più alto tasso di malattie allergiche negli adulti se sono state frequentate regolarmente piscine coperte nell'infanzia, forse per alterazioni dell'epitelio polmonare*
- *Evidenziata un'associazione tra frequentazione di piscine coperte, atopia e rischio di asma nell'infanzia in diversi paesi europei*



## Asmogenicità degli sport

- Nuoto
- Canottaggio
- Sci di fondo
- Pallavolo
- Pallacanestro
- Tennis
- Calcio
- Corsa



Il microclima caldo-umido delle piscine è meno evocativo di sintomatologia asmatica rispetto all'ambiente esterno.

Pediatric Pulmonology 44:31–37 (2009)

State of the Art —

### Swimming Pool, Respiratory Health, and Childhood Asthma: Should We Change Our Beliefs?

Z.S. Uyan, MD,<sup>1</sup> S. Carraro, MD,<sup>1</sup> G. Piacentini, MD,<sup>2</sup> and E. Baraldi, MD<sup>1\*</sup>

**CONCLUSIONS:** Current evidence of an association between childhood swimming and new-onset asthma is suggestive but not conclusive. Important data gaps need to be filled, particularly in exposure assessment and characterization of asthma in the very young. Participants recommended that additional evaluations using a multidisciplinary approach are needed to determine whether a clear association exists.

### **Hazards of chlorine to asthmatic patients**

Sir,

The discussion of the aetiology and management of asthma is a regular feature in the *Journal*. Contrary to the prevalent assumption that swimming is beneficial, a review of my asthmatic patients who swim suggests that in certain individuals, exposure to the irritant fumes of chlorine in the swimming pool contributes to their bronchospasm. This association would be logical in view of the recent developments elucidating the inflammatory pathology of asthma and wartime experience of the toxic effects of chlorine on airway endothelium. Regarding the continuity of the respiratory tract, how many of our chronic wheezy, catarrhal and deaf patients could be exacerbating their condition with a weekly swim in increasingly undiluted bleach?

S P ROTHERY

**British Journal of General Practice, January 1991**

### **Esiste un rischio professionale per gli assistenti bagnanti?**





## Exposure to trichloramine and respiratory symptoms in indoor swimming pool workers

J.H. Jacobs\*, S. Spaan\*, G.B.G.J. van Rooy\*, C. Melfest\*, V.A.C. Zaaij\*,  
J.M. Rooyackers\*,#,\* and D. Heederik\*

**TABLE 7** Comparison of general respiratory symptoms in swimming pool employees and general respiratory symptoms in the general Dutch population, ELON (n=2711), adjusted for age, smoking and sex

General respiratory symptoms	Adjusted
Problems with breathing	2.2 (1.8–2.8)*
Yes, constantly	3.4 (1.9–5.9)*
Frequently, but it always improves	1.3 (1.0–1.7)
Very rarely	2.2 (1.7–2.7)*
Cough during last 12 months	1.3 (1.0–1.7)
Phlegm during last 12 months	1.8 (1.3–2.4)*
Tightness of chest during last 12 months	1.4 (>1.0–1.8)*
Dyspnoea when walking on a flat surface with people of the same age	7.2 (5.2–9.9)*
Wheeze during last 12 months	0.8 (0.6–0.9)
Wheeze and shortness of breath during last 12 months	0.9 (0.7–1.2)
Have you ever had asthma?	2.4 (1.8–3.3)*
Was it doctor diagnosed?	2.1 (1.5–3.0)*
Asthma attack during last 12 months	2.6 (1.5–4.6)*
Woken up by shortness of breath during last 12 months	1.5 (1.1–2.1)*
Shortness of breath after exercise during last 12 months	1.0 (0.7–1.3)
Asthma medication during last 12 months	3.6 (2.4–5.3)*

Data are presented as odds ratio (95% confidence interval). \*: p<0.05.

Occup Environ Med 1998;55:258–263

## Respiratory symptoms and bronchial responsiveness in lifeguards exposed to nitrogen trichloride in indoor swimming pools

N Massin, A B Bohadana, P Wild, M Héry, J P Toamain, G Hubert

**Table 5** Methacholine bronchial challenge (MBC) test in lifeguards (n=334) stratified by measured exposure to nitrogen trichloride (groups 1–4) and by cumulative nitrogen trichloride exposure (groups a–d)

Variable	Group 1	Group 2	Group 3	Group 4	Group a	Group b	Group c	Group d	Total
Male lifeguards (n)	64	69	58	65	63	60	65	70	256
MBC – (n (%))	7 (11.7)	11 (15.9)	13 (22.4)	4 (6.1)	10 (17.3)	12 (20)	8 (12.7)	5 (7.1)	35 (13.7)
Dose-response slope (1/(slope+2.5)) (mean (SD))	0.27 (0.07)	0.28 (0.08)	0.25 (0.09)	0.30 (0.07)	0.27 (0.08)	0.26 (0.09)	0.28 (0.07)	0.28 (0.07)	0.28 (0.08)
Female lifeguards (n)	22	13	17	26	20	24	21	13	78
MBC + (n (%))	13 (59.1)	4 (30.8)	1 (5.9)	4 (15.4)	5 (25)	10 (41.7)	6 (28.6)	1 (7.7)	22 (28.2)
Dose-response slope (1/(slope+2.5)) (mean (SD))	0.19 (0.09)	0.24 (0.11)	0.29 (0.07)	0.27 (0.07)	0.25 (0.08)	0.22 (0.01)	0.27 (0.10)	0.28 (0.07)	0.25 (0.09)

Nella popolazione generale il test alla metacolina puo' essere positivo nel 10% dei casi

## Occupational asthma caused by chloramines in indoor swimming-pool air

K.M. Thickett\*, J.S. McCoach\*, J.M. Gerber†, S. Sadhra†, P.S. Burge\*

**ABSTRACT:** The first series of three workers who developed occupational asthma following exposure to airborne chloramines in indoor chlorinated swimming pools is reported. Health problems of swimmers in indoor pools have traditionally been attributed to the chlorine in the water. Chlorine reacts with bodily proteins to form chloramines; the most volatile and prevalent in the air above swimming pools is nitrogen trichloride.

Two lifeguards and one swimming teacher with symptoms suggestive of occupational asthma kept 2-hourly measurements of peak expiratory flow at home and at work, analysed using the occupational asthma system (OASYS) plotter, and/or had specific bronchial challenge testing to nitrogen trichloride, or a workplace challenge.

Air measurement in one of the pools showed the nitrogen trichloride levels to be 0.1–0.57 mg·m<sup>-3</sup>, which was similar to other studies. Two workers had peak expiratory flow measurements showing occupational asthma (OASYS-2 scores 2.88 and 3.8), both had a positive specific challenge to nitrogen trichloride at 0.5 mg·m<sup>-3</sup> with negative challenges to chlorine released from sodium hypochlorite. The third worker had a positive workplace challenge.

Swimming-pool asthma due to airborne nitrogen trichloride can occur in workers who do not enter the water because of this chloramine. The air above indoor swimming pools therefore needs to be assessed and managed as carefully as the water.

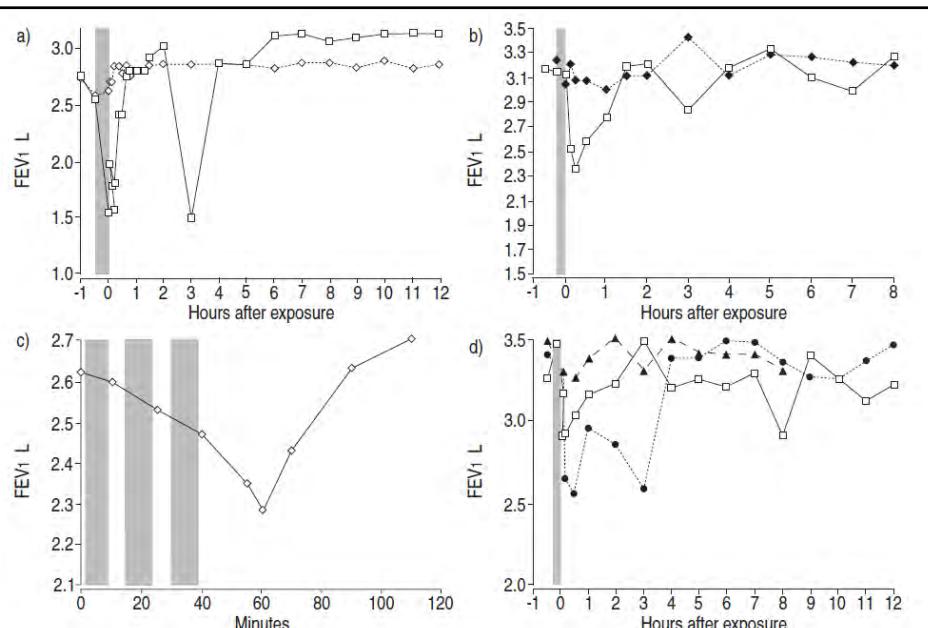


Fig. 2.—Bronchial challenge test to nitrogen trichloride and sodium hypochlorite in a) case one and b) case two. c) Poolside challenge test. d) Bronchial challenge test to nitrogen trichloride (control), water (control) and formaldehyde in an industrial chemist (case four).  
□: nitrogen trichloride; ◆: sodium hypochlorite; ●: formaldehyde; ▲: distilled water. Bars represent the challenge period.

EDITORIAL

**Indoor swimming pools, water chlorination and respiratory health**

B. Nemery\*, P.H.M. Hoet\*, D. Nowak<sup>#</sup>

Until adequate information is available, appropriate ventilation to minimize chloramine accumulation, control of water chlorination and temperature, and adequate hygiene of bathers should be enforced to reduce the irritant nature of swimming-pool environments for both those who work and those who swim there.

**Scopo dello studio**

Scopo di questo lavoro è valutare l'opportunità di una sorveglianza sanitaria per i lavoratori addetti ad impianti di balneazione indoor

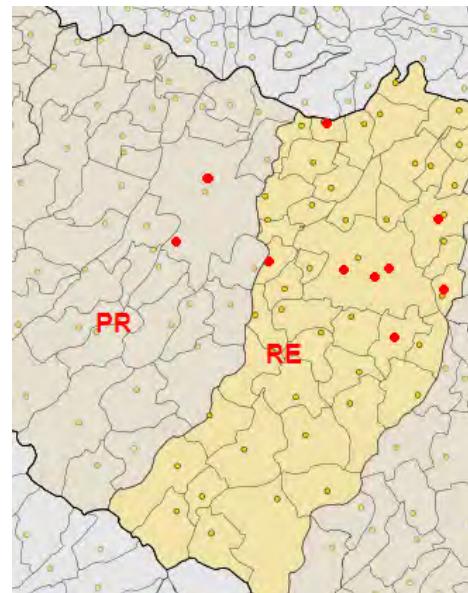
## Campione esaminato

**10 IMPIANTI: PR – RE**

**DATA DI CAMPIONAMENTO:**

**23.03.09 – 28.05.09**

**DISINFEZIONE: CLORO (9) e  
CLORO+UV (1)**



## Soggetti

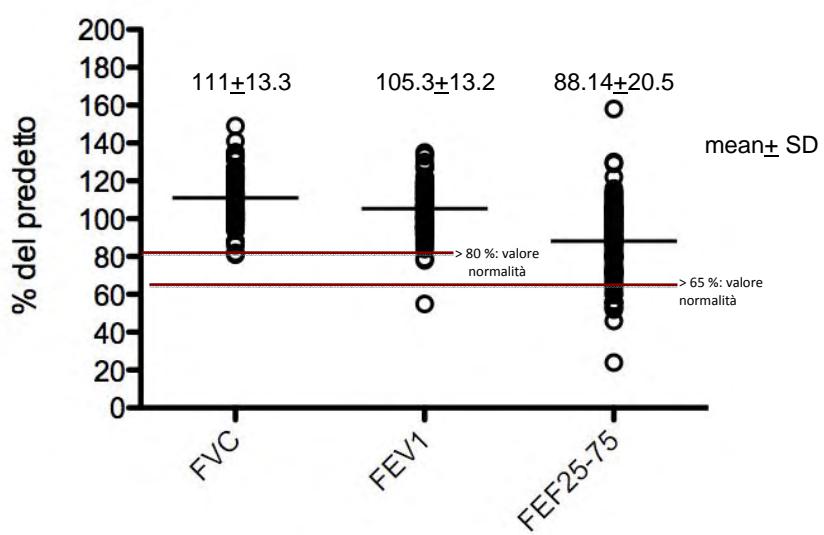
	Maschi	Femmine
n	43	57
Età media ( $\pm$ DS)	33,8 ( $\pm$ 11,5)	33,0 ( $\pm$ 8,0)
Range	19-68	19-59
BSA (body surface area) media ( $\pm$ DS)	1,989 ( $\pm$ 0,145)	1,633 ( $\pm$ 0,138)
Range	1,673- 2,263	1,383- 2,097
Abitudine tabagica media (PY)	3,5	1,0
Media ore settimanali di esposizione	17,0	16,0

## Accertamenti eseguiti

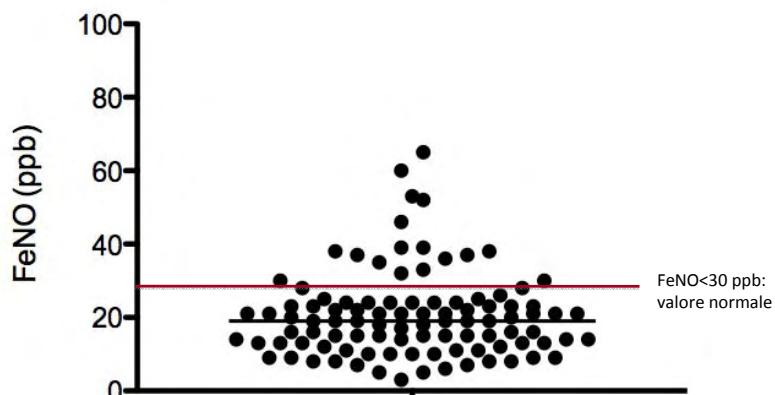
Alla fine di un turno lavorativo, i lavoratori sono stati sottoposti a:

- esame spirometrico
- esame di marcatori nel condensato dell'aria esalata (cloruri, H<sub>2</sub>O<sub>2</sub>, NOx, pH, NH<sub>4</sub><sup>+</sup>)
- esame dell'NO espirato (FeNO<sub>50</sub>)
- questionario anamnestico e clinico

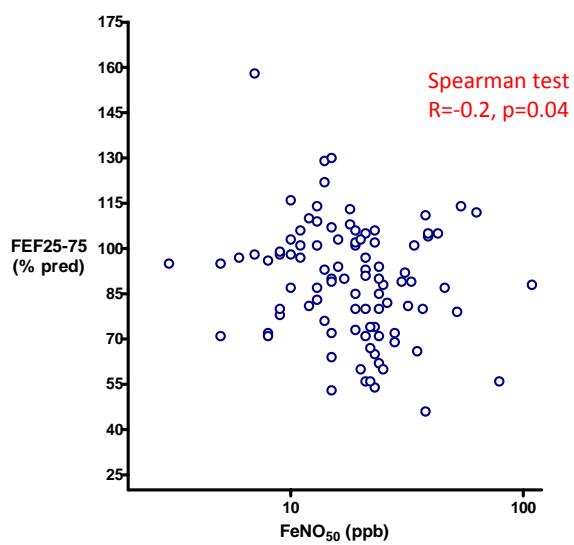
## Esame spirometrico



## FeNO nell'aria esalata



## Correlazione tra FEF<sub>25-75</sub> e FeNO

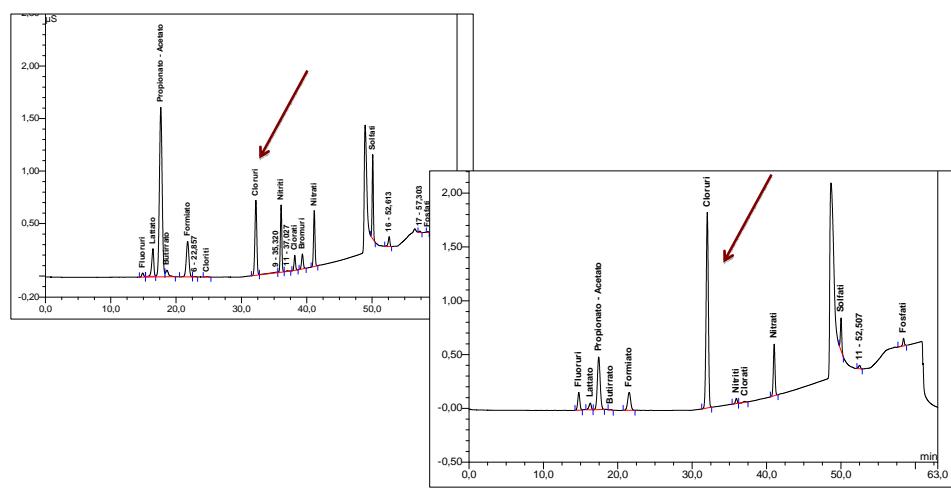


## **Chlorination Products: Emerging Links with Allergic Diseases**

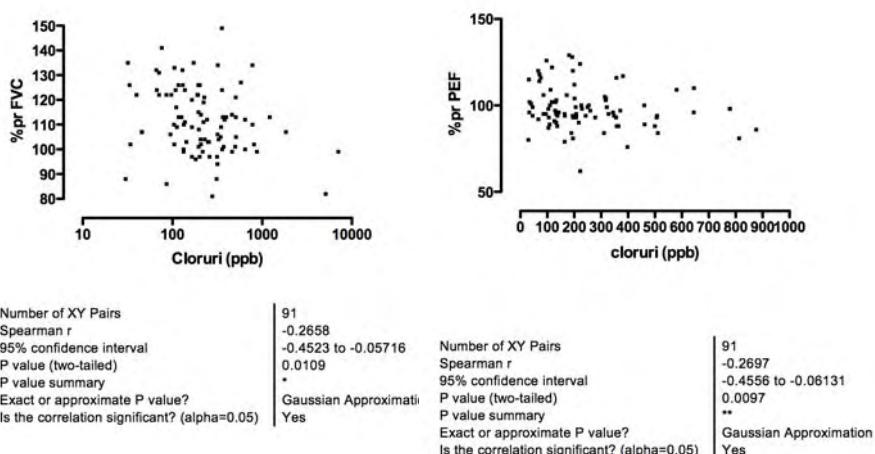
A. Bernard\*

Active or free chlorine	Haloacetonitriles (HCN)
Hypochlorous acid	Dichloroacetonitrile
Hypochlorite	Bromoacetonitrile
<b>Chloramines</b>	Dibromoacetonitrile
Monochloramine	Trichloroacetonitrile
Dichloramine	<b>Haloacetones (HK)</b>
Trichloramine (nitrogen trichloride)	1,1-dichloropropanone
<b>Inorganic by-products</b>	1,1,1-trichloropropanone
Bromate	<b>Chlorophenols</b>
Chlorate	2-Chlorophenol
Chlorite	2,4-Dichlorophenol
Chloride	2,4,6-Trichlorophenol
<b>Trihalomethanes (THM)</b>	Chloropicrin
Chloroform	Chloral hydrate
Bromoform	Cyanogen chloride
Bromodichloromethane	
Dibromochloromethane	

## **La determinazione degli anioni clorurati nel EBC con cromatografo ionico**



## Correlazione tra indicatore di dose e indicatori di effetto



## Discussione

I risultati di questo studio suggeriscono l'opportunità di una sorveglianza sanitaria per i lavoratori addetti alle piscine. Infatti alterazioni spirometriche e biologiche sono presenti anche in soggetti con modeste esposizioni

## **Altre categorie a rischio da esposizione a prodotti clorurati**

- Lavoratori industria alimentare
- Lavoratori industria pulizia
- Produzione del cloro

## **Conclusioni**

L'esposizione a prodotti clorurati sembra essere in grado di:

- **Favorire un fenotipo asmatico in chi frequenta le piscine nell'infanzia**
- **Determinare casi di asma professionale ed asma aggravata dal lavoro**
- **Indurre un effetto subcritico (rilevabile con indicatori di effetto precoci) a livello polmonare in alcuni lavoratori professionalmente esposti**

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