



FMTS



Cleanings agents and disinfectants as irritants and sensitizers

How to evaluate types of bronchial reaction

How to reduce the risks

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DISCLOSURE

In relation to this presentation, I declare the following, real or perceived conflicts of interest :

- **none**

Outline : Cleanings agents and disinfectants : irritant and/or sensitizer ?

① **Definition**

② **Experimental data**

③ **How to evaluate types of bronchial reaction**

④ **How to reduce the risks**

Cleanings agents and disinfectants : irritant and/or sensitizer ?

◆ Sensitizer

- Meaning immunological sensitization IgE, IgG through adaptative immunity and innate immunity

◆ Irritant

" Irritant are non corrosive substances that cause a temporary inflammation on direct contact " USA Occupational Safety and Health Administration (OSHA)

- ✓ Intensity, duration sufficient ⇒ Inflammatory and remodeling process

Cleanings agents and disinfectants : irritant and/or sensitizer ?

- ◆ **Actions of an irritant → non specific but**
 - **Activation and recruitment of inflammatory and immunocompetent cells :**
 - ✓ **Epithelial damage**
 - ✓ **Proinflammatory responses**
 - ✓ **Neurogenic inflammation**
 - ✓ **Increased bronchial permeability**
 - ✓ **Remodeling airway epithelium**

Outline : Cleanings agents and disinfectants : irritant and/or sensitizer ?

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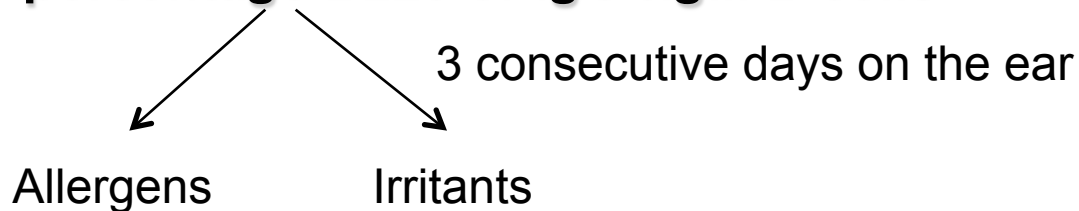
Cleanings agents and disinfectants : irritant and/or sensitizer ?

◆ Pathophysiology : Animal - irritant vs sensitization

● : Mice CBA/J

✓ Contact to allergens

- ↗ B cell activation
- Local lymph nodes
- ↗ percentage B220 or IgG⁺/IgM B cells



Flow cytometric Analysis Significant increase B 220⁺ B cells No increase

Allergen : ratio B 220⁺ cells chemical / B220⁺ cells vehicle > 1.25

Irritant : ratio < 1.25

Cleanings agents and disinfectants : irritant and/or sensitizer ?

◆ Pathophysiology : Animal

Classification of Allergens and Irritants Using the Test:Vehicle B220 Ratio (Laboratory 1)

Treatment	No. experiments	Test:vehicle ratio		Correctly classified
		Cells/node	% B220 ⁺ cells	
Allergens				
DNCB (0.25% in ACE)	17	7.72 ± 1.84	2.91 ± 0.82	17/17 (100%)
TNCB (0.5% in ACE)	3	11.00 ± 5.66	2.89 ± 0.99	3/3 (100%)
ISOE (5% in ACE)	4	2.70 ± 0.78	2.00 ± 0.61	4/4 (100%)
EUG (25% in ACE)	4	3.20 ± 0.78	2.38 ± 0.43	4/4 (100%)
HCA (50% in ACE)	13	4.06 ± 1.43	1.93 ± 0.74	12/13 (92.3%)
Irritants				
→ BZC (2% in ACE)	13	3.82 ± 1.19	1.03 ± 0.37	11/13 (84.6%)
SLS (20% in 20% ETOH)	6	1.39 ± 0.37	1.02 ± 0.13	6/6 (100%)
MS (10% in AOO)	5	1.50 ± 0.13	1.09 ± 0.06	5/5 (100%)
SA (40% SA in ACE)	4	1.86 ± 0.44	1.44 ± 0.31	2/4 (50.0%)

Note. Values presented as mean ± SD.

BAC (2 %) was considered as an irritant

Cleanings agents and disinfectants : irritant and/or sensitizer ?

◆ Experimental data : Animal

- Atopic dermatitis in NC/Nga mice

① Injection of mite allergen (Dpt) → skin lesion

② Application at the same time:

Benzalkonium chloride 0.2 %

Povidone Iodine 10 %

Ethanol 80 %

Chlorhexidine 0.5 %

Cleanings agents and disinfectants : irritant and/or sensitizer ?

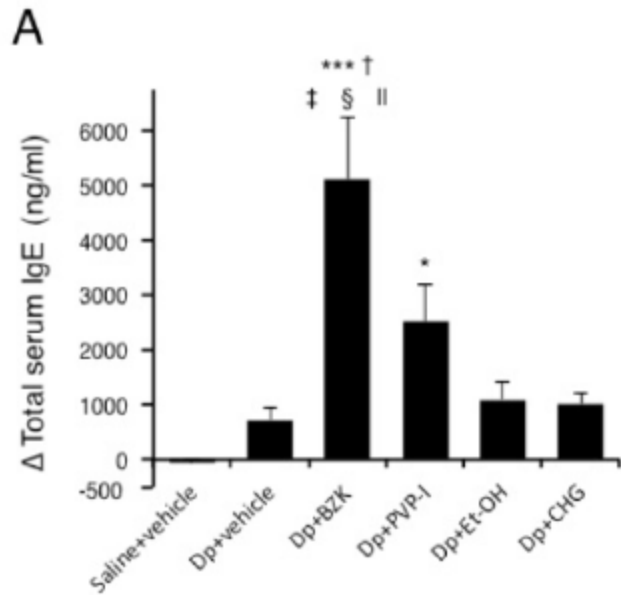


Figure 6. Immunoglobulins levels in the serum of NC/Nga mice. (A) Total IgE and (B) Dp-specific IgG₁ levels. Sera were collected by orbital puncture at one day before the first immunization (for IgE) and cardiac puncture on the last day of the experiment (for IgE and IgG₁), and assayed by ELISA. Results are mean \pm SE values of 12 mice. * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ vs. saline + vehicle group. † $p < 0.001$ vs. Dp + vehicle group. ‡ $p < 0.05$ vs. Dp + PVP-I group. § $p < 0.001$ vs. Dp + Et-OH group. || $p < 0.001$ vs. Dp + CHG group.

Cleanings agents and disinfectants : irritant and/ or sensitizer ?

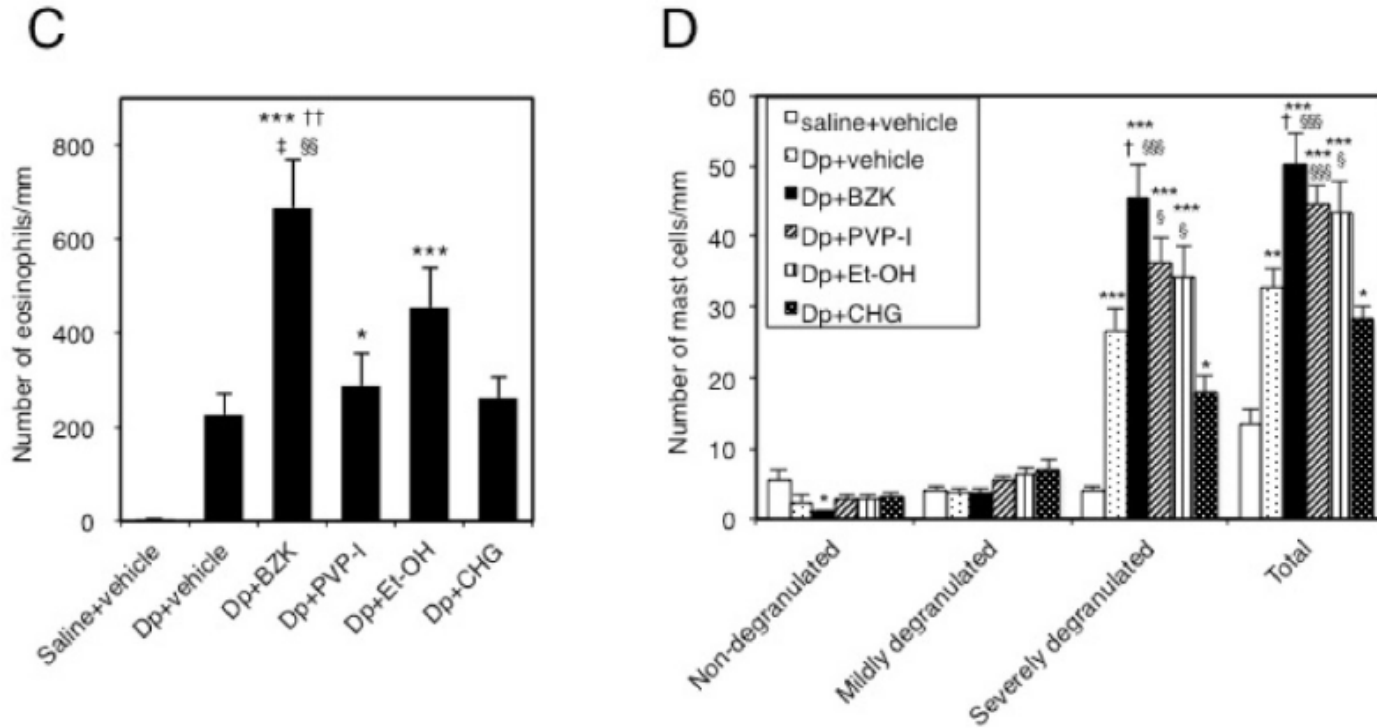


Figure 4. Histological changes in mouse ear tissue on day 18. Microscopic view of ear sections stained with (A) hematoxylin and eosin (HE; scale bar = 40 μ m) or (B) toluidine blue (TB; scale bar = 40 μ m). Number of eosinophils (C) and mast cells (D) in ear tissue stained with HE and TB. The numbers of inflammatory cells in 9 areas that extended perpendicularly from the edge of the cartilage of the external ear by a length of 100 μ m (eosinophils) or 400 μ m (mast cells) to the epidermal layer were counted. Mast cells were classified as non-degranulated (0%), mildly degranulated (0–50%), or severely degranulated (>50%) according to the severity of degranulation. Data are the mean \pm SE values of 6 mice in (B) and (C). * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$ vs. saline + vehicle group. † $p < 0.01$, and †† $p < 0.001$ vs. Dp + vehicle group. ‡ $p < 0.01$ vs. Dp + PVP-I group. § $p < 0.05$, §§ $p < 0.01$, and §§§ $p < 0.001$ vs. Dp + CHG group.

Cleanings agents and disinfectants : irritant and/or sensitizer ?

◆ Immunological reactivity :

● Specific IgE to quaternary ammonium :

✓ n = 583 (health care workers)

➤ 7 % : detectable IgE to QAT

➤ No relation with symptoms

✓ 3 cases reported with positive SIC to QAT

➤ No specific IgE to quaternary ammonium

● Ig E demonstrated for Chloramine T, enzymes

Purohit A. et al, Int. Arch. Occup. Environ. Health, 2000.

Gonzales M. et al, Clin Exp Allergy 2013.

Cleanings agents and disinfectants : irritant and/or sensitizer ?

- ◆ **Sensitizer : adjuvant effect in human**
 - 194 pig farmers (at least 5 h / day)
 - 124 farmers with NSBH test to histamine
 - Use of QACs (less than 15 min / week)
 - Personal endotoxin dust samples were performed
 - Atopy : more than one positive specific IgE to common allergens

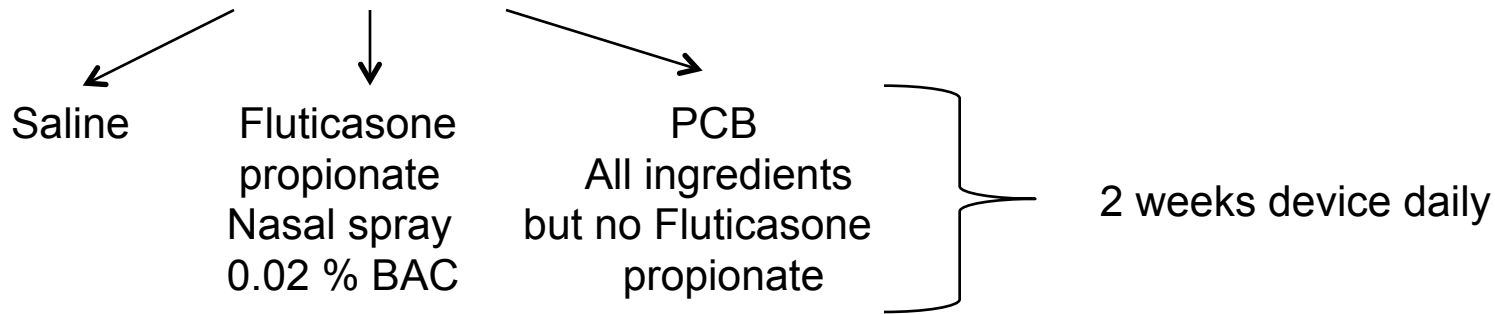
Cleanings agents and disinfectants : irritant and/or sensitizer ?

- ◆ **Sensitizer : adjuvant effect in human**
 - **Use of QACs : increase atopy OR = 7.4 [1.3 - 43.1]**
 - **Use of other disinfectant : non significant**
 - **No effect of exposure to endotoxin**

Cleanings agents and disinfectants : irritant and/or sensitizer ?

◆ Experimental data : Human

● 65 volunteers



● Results : No difference in the 3 groups

- ✓ Symptoms scores
- ✓ Acoustic rhinometry
- ✓ Saccharin clearance time
- ✓ Ciliary beat frequency

BAC seems to have no effect on the human nasal mucosa

Cleanings agents and disinfectants : irritant and/or sensitizer ?

◆ Epidemiology : Swimming pool

● Children :

✓ Discrepancies between :

- **Swimming pool attendance in the first year of life and higher rates of atopic disease**

Bernard A. et al, Environ. Health Perspect., 2006.
Schoefer Y. et al, Int. J. Hyg. Envir. Health, 2008.

- **Swimming pool attendance before the age of 2 y. vs after 4 y. o.**

Asthma : OR : 0.79 [0.43 - 1.46]

Rhinitis : OR : 0.86 [0.68 - 1.08]

Slightly less upper and lower respiratory tract symptoms

Cleanings agents and disinfectants : irritant and/or sensitizer ?

◆ Epidemiology : Swimming pool

● Pool workers :

- ✓ 624
- ✓ 38 swimming facilities
- ✓ Chloramine measurement (2h)
- ✓ Work related symptoms
- ✓ Atopy
- ✓ Bronchial hyperresponsiveness

Cleanings agents and disinfectants : irritant and/or sensitizer ?

◆ Epidemiology : Swimming pool

● Pool workers :

✓ Higher exposure → upper respiratory symptoms

➤ Hoarseness : OR : 1.6 [1.2 – 2.1]

➤ Lost voice : OR : 1.5 [1.1 – 2.0]

➤ Sinusitis : OR : 1.4 [>1.0 – 1.8]

● Pool workers vs Dutch population: more general respiratory symptoms: OR: 1.4-7.2

Outline : Cleanings agents and disinfectants : irritant and/or sensitizer ?

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Cleanings agents and disinfectants : irritant and/or sensitizer ?

◆ Symptoms : New onset of asthma

- ✓ 43 female domestic cleaners (aged 49)
- ✓ Recent history of asthma :
 - Asthma attack
 - Shortness of breath
- ✓ Chronic bronchitis
- ✓ Daily change in symptoms and PEF
- ✓ Diagnosis based

{	<ul style="list-style-type: none">- on computerised diagnosis system- on expert occupational asthma
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- ✓ 2 weeks study

Cleanings agents and disinfectants : irritant and/or sensitizer ?

◆ Symptoms :

- Lower respiratory symptoms related with working day

	OR [IC]
✓ Exposure to bleach	2.5 [1.1-5.8]
✓ Degreasing spray	2.6 [1.1-6.6]
✓ Air fresheners spray	6.5 [2.1-20]

Only 30% scored positively of occupational asthma

Cleanings agents and disinfectants : irritant and/or sensitizer ?

◆ Diagnosis of Irritant Induced Asthma :

- (Nested) case-control study of female cleaners (30-65 y)
- 40 cases (asthma or chronic bronchitis) – 155 controls
 - ✓ Higher risk of asthma if use of bleach (dose-related)
 - ✓ Higher risk of asthma if reported inhalation incident (frequent !)
- RADS
 - ✓ Inadequate mixture of bleach with ammonia or hypochloria acid → free chlorine or chloramine

Cleanings agents and disinfectants : irritant and/or sensitizer ?

Multivariate associations (adjusted odds ratios and 95% confidence intervals) between asthma/chronic bronchitis symptoms, and risk factors

	Controls (n = 152*)	All cases (n = 40)	OR (95% CI)	Asthma (n = 24)	OR (95% CI)	Chronic bronchitis without asthma (n = 16)	OR (95% CI)
Bleach (both undiluted and diluted)							
<364 times/year	56	8	1.0	3	1.0	5	1.0
364-640 times/year	53	11	3.3 (0.9 to 11)	9	10 (1.7 to 60)	2	0.9 (0.1 to 6.5)
≥640 times/year	43	21	4.9 (1.5 to 15)	12	12 (2.3 to 67)	9	2.6 (0.6 to 12)
Use of liquid multi-use cleaning products							
<266 times/year	50	20	1.0	13	1.0	7	1.0
266-480 times/year	51	12	0.3 (0.1 to 0.8)	6	0.2 (0.0 to 0.7)	6	0.3 (0.1 to 1.6)
≥480 times/year	51	8	0.2 (0.1 to 0.6)	5	0.1 (0.0 to 0.5)	3	0.2 (0.0 to 1.3)
Washing dishes							
<376 times/year	64	10	1.0	8	1.0	2	1.0
376-520 times/year	37	12	3.2 (1.0 to 10)	6	2.0 (0.5 to 8.9)	6	7.5 (1.0 to 53)
≥520 times/year	51	18	3.1 (1.1 to 8.9)	10	3.8 (1.0 to 14)	8	6.5 (0.9 to 47)
Inhalation of an important quantity of vapours, gas, or fumes related to cleaning agents							
Never	73	9	1.0	5	1.0	4	1.0
Ever	79	31	2.3 (0.9 to 6.1)	19	3.8 (1.0 to 14)	12	0.9 (0.2 to 4.3)
Employment in non-domestic cleaning							
Never	101	9	1.0	5	1.0	4	1.0
Ever	51	31	8.5 (3.2 to 23)	19	12 (3.2 to 46)	12	7.9 (1.6 to 39)
Smoking							
Never	127	25	1.0	19	1.0	6	1.0
Currently	15	11	4.1 (1.1 to 15)	2	0.5 (0.1 to 3.9)	9	22 (3.6 to 137)
Formerly	10	4	5.3 (1.1 to 25)	3	5.5 (0.9 to 33)	1	8.9 (0.5 to 173)

Multiple logistic regression analyses adjusted for all listed variables and age tertile.

*Three controls had missing values for one or more of the exposure variables and were not included in this multivariate model.

Cleanings agents and disinfectants : irritant and/or sensitizer ?

- ◆ **Symptoms : Work exacerbated asthma**
 - **25 women with asthma vs 19 without asthma**
 - **12 weeks study**
 - **No effect on PEF :**
 - ✓ **After cleaning, in the 2 groups**
 - **Change in number of lower respiratory symptoms**
 - ✓ **Significant in the asthma groups**

Cleaning activities → increased lower respiratory symptoms in asthmatic (independently of the chemical, severity of exposure, duration of cleaning).

Cleanings agents and disinfectants : irritant and/or sensitizer ?

- ◆ **Symptoms : Work associated irritable larynx syndrome (WILS)**
 - **Episode of dyspnoea, dysphonic**
 - **Cough, sensation of tension in the throat**
 - **Female**
 - **More frequently report of gastro-oesophageal reflux**
 - **Triggers = odours, fumes, perfumes, cleaning agent**

Cleanings agents and disinfectants : irritant and/or sensitizer ?

◆ Diagnosis

- Measure non specific airway hyperactivity

- ✓ Adults (age : 32)

- ✓ 10 {
 - 5 HR : PD₂₀ methacholine 0.6 ng/mL
 - 5 normal : PD₂₀ methacholine 38.0 ng/mL

- ✓ Exposed to 1.0 ppm chlorine (ceiling short term exposure) for 60 min

Cleanings agents and disinfectants : irritant and/or sensitizer ?

◆ Non specific airway hyperactivity

*Responses to 1.0 ppm Chlorine Inhalation:
Normal Compared With Hyperreactive Subjects**

Pulmonary Function Change From Baseline	Normal, Mean ± SD	HR, Mean ± SD	p Value
FEV₁			
Absolute change, mL	-180 ± 84	-520 ± 383	0.04
Relative change, %	-4 ± 2	-16 ± 13	0.01
FVC			
Absolute change, ml	-20 ± 84	-420 ± 460	0.06
Relative change, %	-0.4 ± 1	-9 ± 11	0.06
FEF₂₅₋₇₅			
Absolute change, mL/s	-400 ± 255	-540 ± 378	0.83
Relative change, %	-11 ± 8	-25 ± 20	0.14
PEFR			
Absolute change, L/s	-0.4 ± 0.5	-1.4 ± 1.3	0.06
Relative change, %	-5 ± 6	-18 ± 16	0.09
Sraw			
Absolute change, U	+2.1 ± 1.6	+7.5 ± 4.9	0.04
Relative change, %	+39 ± 28	+108 ± 93	0.09

*HR=hyperreactive subjects defined by methacholine responsiveness;
HR compared with normal subjects, differences tested by Wilcoxon
ranked sum test.

**But no change with 0.4
ppm chlorine.**

Patients with NSHR manifest an exaggerated airway response to chlorine at 1.0 ppm.

Cleanings agents and disinfectants : irritant and/or sensitizer ?

◆ Diagnosis : Specific inhalation challenge

- 4 patients / 13 → positive SIC (0.4 ppm)
 - 2 late phase reaction
 - 1 dual reaction
 - 1 with an increase of PC 20 methacholine of one doubling dose
- 6 negative controls
- No change in FeNO
- No change in induced sputum

No difference between patient with or without NSHR to metacholine for positivity to SIC.

Cleanings agents and disinfectants : irritant and/or sensitizer ?

◆ Irritants : human

- **Effects of Ipratropium bromide and sodium cromoglycate**
- **9 patients with atopic mild asthma**
- **Pre inhalation of ipratropium bromide (0.25 mg / mL to 1 mg/mL) or 0.9 % saline, same day 2 separate occasions**
- **Pre-inhalation of sodium cromoglycate (10 mg / mL) or Saline**
- **45 minutes after dose response to BAC (0.4 - 50 mg / mL)**

Cleanings agents and disinfectants : irritant and/or sensitizer ?

◆ Results :

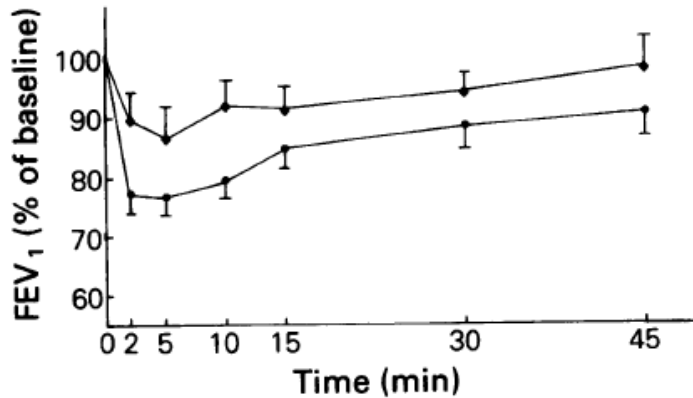


Figure 1 The effect of pretreatment with inhaled saline (●) and ipratropium bromide 1 mg (◆) on airway calibre following inhalation of benzalkonium chloride by 9 asthmatic subjects. Each point represents the mean FEV₁ expressed as percent of post-treatment baseline and each bar the SEM.

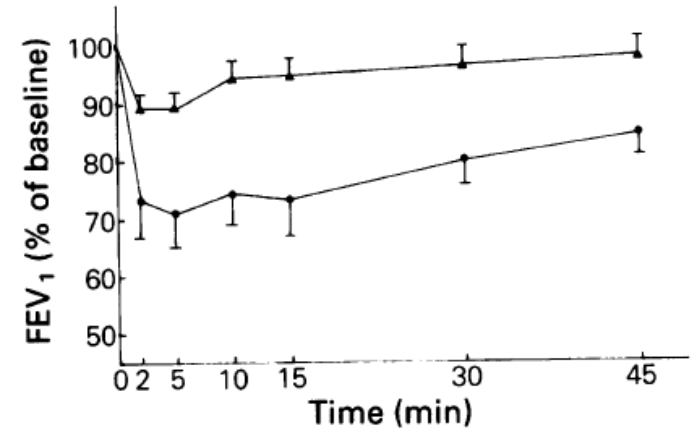


Figure 2 The effect of pretreatment with inhaled saline (●), and sodium cromoglycate 40 mg (▲) on airway calibre following inhalation of benzalkonium chloride by eight asthmatic subjects. Each point represents the mean FEV₁ expressed as percent of post-treatment baseline and each bar the s.e. mean.

Bronchoconstriction in asthmatic induced by BAC was obtained though a combination of mast cells activation and stimulation of peripheral and central neural pathways.

Quaternary ammonium : specific inhalation challenges

	POSITIVE SIC	NEGATIVE SIC
Gender (%)	12 (10 women)	10 (10 women)
Mean age (SD)	47.6 (\pm 6.9)	45.8 (\pm 9.1)
Atopy (%)	5 (45)	3 (30)
Rhinitis (%)	8 (73)	5 (50)
Conjunctivitis (%)	4 (36)	3 (30)
Baseline FEV 1 (%) [range]	100 [66 – 114]	97 [79 – 117]

Bellier M. et al, JACI in practice 2015.

Cleanings agents and disinfectants : irritant and/ or sensitizer ?

TABLE II. SIC characteristics

Characteristic	Positive SIC (n = 12)	Negative SIC (n = 10)
Type of QAC (n)		
Didecyl dimethyl ammonium chloride	9	7
Alkyl dimethyl benzyl ammonium chloride	1	
Didecylmethyl ammonium propionate		1
Benzalkonium chloride	2	1
Bis-aminopropyl-laurylamine and amine oxide		1
Immediate bronchial response (n)	7	NA
Mean fall in FEV ₁ (%)	23.4 ± 5.7	NA
Mean duration of exposure (min)	18.5 ± 14	NA
Median duration of exposure (min)	15 ± 13	NA
Rhinitis (n)*	8	3
Metacholine inhalation test (n)	5	10
Mean maximum fall in FEV ₁ during SIC in patients who underwent a metacholine inhalation test (%)	8.8 ± 2.8	7.9 ± 3.5

NA, Not applicable.

Data are presented as n or as mean or median ± SD.

**P* > .05 (Fischer exact test).

There was no difference between patients with a positive or a negative SIC .

SIC seems necessary to make the diagnosis of OA to QATs

Cleanings agents and disinfectants : irritant and/or sensitizer ?

Table 2 Changes in non-specific airway responsiveness and sputum cells during inhalation challenges with cleaning agents

	Positive SIC			Negative SIC		
	Baseline	Postchallenge	p Value	Baseline	Postchallenge	p Value
AHR to histamine	(n=17)	(n=12)		(n=27)	(n=25)	
PC ₂₀ , mg/mL	1.4 (0.2–4.22)	0.5 (0.4–3.0)*	0.019	13.0 (1.4–32.0)	16.9 (2.6–32.0)	0.267
PC ₂₀ >16 mg/mL†	2 (12)	0		13 (48)	13 (52)	
>Threefold decrease in PC ₂₀ †		5 (42)			0	
Sputum cell counts‡	(n=13)	(n=13)		(n=7)	(n=7)	
Total cell count, 10 ⁶ /mL	0.54 (0.34–0.97)	1.15 (0.53–2.17)	0.041	0.34 (0.26–1.89)	0.65 (0.38–1.81)	0.735
Eosinophils, 10 ⁶ cells/mL	0.02 (0.01–0.04)	0.12 (0.02–0.39)	0.006	0 (0–0.01)	0 (0–0.01)	0.345
Eosinophils, %	1.8 (0.8–7.2)	10.0 (4.1–15.9)	0.009	0.2 (0–2.5)	0.8 (0.2–1.5)	0.786
Increase in eosinophils >2%†		8 (62)			0	
Neutrophils, 10 ⁶ cells/mL	0.40 (0.17–0.70)	0.71 (0.38–1.62)	0.009	0.19 (0.16–1.70)	0.34 (0.25–1.52)	0.866
Neutrophils,%	57.3 (42.4–72.5)	69.5 (56.9–83.0)	0.152	60.3 (55.7–83.0)	70.3 (52.5–84.0)	0.866

Data are presented as median value with 25–75th IQR in parentheses unless otherwise specified.

*Histamine PC₂₀ was measured at 7 h after the end of exposure in six participants and 24 h postexposure in six participants with positive SIC.

†Data expressed as n (% of available data).

‡Data available on participants who performed an SIC from 2006 onwards.

AHR, airway hyper-responsiveness; PC₂₀, provocative concentration of histamine causing a 20% fall in FEV₁; SIC, specific inhalation challenge.

Patients who had a positive SIC were more severe: higher obstruction and more frequent use of beta 2 agonists

Patients with a positive SIC had an increase in NSHR and in eosinophils suggesting a « sensitization ».

Outline : Cleanings agents and disinfectants : irritant and/or sensitizer ?

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Cleanings agents and disinfectants : irritant and/or sensitizer ?

◆ Primary prevention

● Avoidance specific exposure :

- ✓ Avoid mixing bleach + Ammonium
 - ✓ Avoid to use bleach in non ventilated room
 - ✓ Avoid to spray
 - ✓ Avoid glutaraldehyde → change to a less volatile ortho-phthalaldehyde
 - Use product non sprayed but wiped and with low volatility
- ⇒ ↘ asthma

Cleanings agents and disinfectants : irritant and/or sensitizer ?

◆ Primary prevention

- Use « green products »

- But they are not necessarily safer for inhalation

- *USA EPA Website :*

- <https://www3.epa.gov/epp/pubs/guidance/standards.htm>

- Computerized quantitative structure activity program

- ⇒ Predict possible sensitizing potential

RM Agius +++++

Cleanings agents and disinfectants : irritant and/or sensitizer ?

◆ Secondary prevention

- Records of incidents workplace**
- Analyse group results to identify problem exposure**
- Replacement agent less hazardous**
- Health education**
- Protective respiratory devices**

Cleanings agents and disinfectants : irritant and/or sensitizer ?

- ◆ **Early recognition of possible WRA**
 - **14 items self administered screening questionnaire**
 - **Good reproducibility**

Cleanings agents and disinfectants : irritant and/or sensitizer ?

- ◆ **Education – Information**
- ◆ **Cleaning enterprises (Norway)**
- ◆ **Chemical health hazards**
- ◆ **Definition of a conceptual risk level**
- ◆ **322 enterprises → 8 300 workers**
 - **9 % no training programs**
 - **65 % had difficulties due to poor language**
 - **No difference between small and large enterprises**

Cleanings agents and disinfectants : irritant and/or sensitizer ?

- Behavioural-related interventions for reducing exposure to dermal and respiratory occupational health hazards in workers have had a limited impact upon exposure.
- A lack of effectiveness could be explained by either methodological shortcoming in intervention design, under-reporting or inadequate coverage of the behaviour change ‘ingredients’ necessary for improving safe practices.

Conclusion

- ◆ **The cleaning or disinfectant products could induce sensitization and irritation.**
- ◆ **Specific inhalation challenge appears to be necessary to make the diagnosis.**
- ◆ **For QATs, it seems that a positive SIC corresponds to a sensitization mechanism but more studies are needed to confirm the preliminary results.**

Conclusion

- ◆ **For chlorine, the data seem less convincing for a sensitization mechanism, however larger studies are needed.**
- ◆ **Neurogenic inflammation appears to be a possible mechanism.**
- ◆ **About prevention, behavioural-related interventions seem to be efficient .**
- ◆ **It is mandatory to avoid sprays and to associate different method to decrease the exposure.**

Aknowledgment

Pôle de pathologie thoracique

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Cleaning agents : Specific inhalation challenge

◆ Results

- Patient with a positive SIC
 - ✓ Use more often of β_2 agonists
 - ✓ use of higher doses of inhaled corticosteroids
 - ✓ Lower baseline FEV 1
 - ✓ More baseline airway obstruction (FEV1/FVC<70%, FEV1<80%)

Vandenplas O. et al, iBMJ open in press