

Chlorination Products: Emerging Links with Allergic Diseases

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Abstract: Exposure of the human population to chlorination products has considerably increased during the 20th century especially after the 1960s with the development of public and leisure pools. The present article summarizes current knowledge regarding the human exposure to chlorination products and reviews studies suggesting that these chemicals might be involved in the development or exacerbation of allergic diseases. Populations regularly in contact with chlorination products such as swimmers, lifeguards or workers using chlorine as cleaning or bleaching agent show increased risks of allergic diseases or of respiratory disorders frequently associated with allergy. Experimental evidence suggests that chlorination products promote allergic sensitization by compromising the permeability or the immunoregulatory function of epithelial barriers. These findings led to the chlorine hypothesis proposing that the rise of allergic diseases could result less from the declining exposure to microbial agents (the hygiene hypothesis) than from the increasing and largely uncontrolled exposure to products of chlorination, the most widely used method to achieve hygiene in the developed world. Giving the increasing popularity of water recreational areas, there is an obvious need to assess the effects of chlorine-based oxidants on human health and their possible implication in the epidemic of allergic diseases.

Keywords: Chlorine, hypochlorite, chloramines, allergy, asthma, chlorinated pool, chlorination.

The water chlorination process is intimately linked to hygiene and is considered as one of the greatest advances in public health of the 20th century. In the developed world, the routine chlorination of water supplies has indeed led to the virtual eradication of waterborne diseases such as typhoid fever, cholera or dysentery, which undoubtedly has contributed to increase human longevity. Nowadays, chlorine-based disinfectants are used in a wide variety of applications such as sanitation of drinking and recreational water, disinfection in the food industry or cleaning of surfaces in public and private buildings. Advantages of chlorine include low cost, easy use, residual protection, deodorising and a strong germicide activity against a wide spectrum of microorganisms [1].

Interestingly, hypochlorous acid, the active biocide in chlorination, is also part of the arsenal used by the immune system to fight infections. Hypochlorous acid is indeed a chemical weapon produced by specialized cells of the immune system (polymorphonuclear cells) to kill bacteria. Similarly to what happens during water chlorination, hypochlorous acid reacts with cellular amines to form long-lived oxidants such as monochloramine. Both hypochlorous acid and monochloramine, at non cytotoxic concentrations, also cause a rapid and reversible disruption of cellular junctions of the epithelial layers, which facilitates the migration of inflammatory cells across the epithelial or endothelial barriers [2-4].

Chlorine as a disinfectant has, however, two drawbacks. The first is that chlorine is a non-specific biocide and when used in drinking or recreational water, its concentration must be carefully controlled. Second, when added to water, chlorine transforms organic contaminants into a mixture of potentially harmful products that can be absorbed by inhalation, ingestion and across the skin [5-6]. The discovery that some of these by-products, the trihalomethanes (THM) in particular, are potent mutagens led to considerable research in order to assess the risks of cancer associated with the consumption of chlorinated water. Epidemiological studies suggest that long-term exposure to chlorination products (CPs) via drinking water and perhaps also via bathing water can increase the risk of bladder cancer [7-8]. Although the population attributable risk might be important in industrialized countries, there is a consensus among scientists and regulatory bodies to say that the

carcinogenic risks posed by CPs remain very small compared to the risks of inadequate disinfection. By contrast, although being much more concentrated in chlorinated water than THM, chlorine-based oxidants have received very little attention, even in the most recent risk assessments [5, 6]. These chemicals, however, have suddenly come under scrutiny with the unexpected finding that regular attendance of indoor swimming pools was associated with an exposure-dependent increase in lung epithelium permeability and in the risk of developing asthma [9-14]. This chapter reviews the evidence linking CPs to the development of allergic diseases or of respiratory disorders having frequently an allergic component. The mechanisms by which these chemicals could promote allergic sensitization and their possible implication in the worldwide epidemic of allergic diseases are also discussed. The review has been conducted by targeting publications in the peer-review literature using as key words chlorine, chlorinated, trichloramine or chloramine in combination with allergy, respiratory, asthma, eczema or permeability. Because of the paucity of data published before the 2000s, research letters and correspondence were also considered.

THE CHEMISTRY OF CHLORINATION

Chlorination is the process of adding small amounts of chlorine to water in order to make it safe for human consumption or for bathing, swimming and other activities. Chlorine can be added to water as gaseous chlorine (or dichlorine) that hydrolyzes almost completely to form hypochlorous acid, hydrogen ion and chloride. Chlorine can also be added in water as calcium hypochlorite ($\text{Ca}(\text{OCl})_2$, solid), lithium hypochlorite (LiOCl , solid) or sodium hypochlorite (NaOCl , liquid, bleach). It can also be added in the form of sodium dichloroisocyanurates, a stabilized form of chlorine largely used as tablets in backyard swimming pools. All these chlorine-based disinfectants loosely referred to as chlorine once added to water release hypochlorous acid. The latter is a weak acid with a pKa of 7.5 at 25°C that reversely dissociates into hypochlorite and hydrogen ion. It is believed that the negative charge on the hypochlorite ion hinders its passage across bacterial membranes and thus that the most active biocide able to oxidize vital cellular components is probably hypochlorous acid. When reacting with organic or inorganic matter in water, hypochlorous acid generates a very complex mixture of chlorination by-products. Actually, there are hundreds chlorination by-products, the majority of them has

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not yet been identified. Table 1 lists some of the most studied types of CPs. Among these chemicals, those with the strongest oxidizing potential are chlorine gas, hypochlorous acid and chloramines. The latter are formed as a result of the chlorination of nitrogen according to the following reactions [15]:

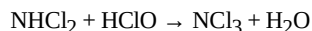
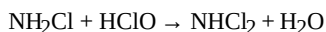
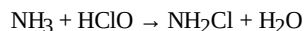


Table 1. Active Chlorine, Chloramines and Disinfection by-Products

Active or free chlorine	Halocetonitriles (HCN)
Hypochlorous acid	Dichloroacetonitrile
Hypochlorite	Bromochloroacetonitrile
Chloramines	Dibromoacetonitrile
Monochloramine	Trichloroacetonitrile
Dichloramine	Haloketones (HK)
Trichloramine (nitrogen trichloride)	1,1-dichloropropanone
Inorganic by-products	1,1,1-trichloropropanone
Bromate	Chlorophenols
Chlorate	2-Chlorophenol
Chlorite	2,4-Dichlorophenol
Chloride	2,4,6-Trichlorophenol
Trihalomethanes (THM)	Chloropicrin
Chloroform	Chloral hydrate
Bromoform	Cyanogen chloride
Bromodichloromethane	
Dibromochloromethane	
Haloacetic acids (HAA)	
Monochloroacetic acid	
Dichloroacetic acid	
Trichloroacetic acid	
Monobromoacetic acid	
Dibromoacetic acid	
Dichlorobromoacetic acid	
Chlorodibromoacetic acid	
Tribromoacetic acid	

Chloramines formed during chlorination include thus the chloramide (monochloramine, NH_2Cl), the chlorimide (dichloramine, NHCl_2) and the nitrogen trichloride (trichloramine, NCl_3). Nitrogen trichloride is predominant at pH <8 and when the chlorine/nitrogen ratio is high. From the Henry's constants of the different chloramines, it can be inferred that nitrogen trichloride is the species most likely to be found in highest concentrations in the air of indoor swimming pools whereas the mono- and dichloramines can be present in significant amounts only in the form of aerosols [16, 17]. Chloramines in water are referred to as combined chlorine, which basically corresponds to the sum of the concentrations of the mono- and dichloramine. Monochloramine is also a chlorine-based disinfectant used in some countries to avoid the formation of THMs. The two other chloramines are nuisances irritating the eyes, the skin and the upper respiratory tract.

Trichloramine also gives indoor pools their distinctive odour that people wrongly attribute to chlorine.

HUMAN EXPOSURE TO CHLORINATION PRODUCTS

Although the purifying and disinfecting properties of hypochlorite or chlorine bleach were established more than 150 years ago, human exposure to CPs really started with the use of chlorine to disinfect drinking water [18, 19]. One of the first known uses of chlorine for water disinfection was by John Snow in 1850 when he attempted to disinfect the Broad Street pump Water supply in London after an outbreak of cholera. The continuous use of chlorine for chlorination of drinkable water began in the early years of the 20th century. In 1902, the town of Middelkerke in Belgium was the first to use on routine basis chlorine to sanitize drinking water (anecdotally, this small town on the Northern sea coast is only thirty miles away from the city of Ypres, also in Belgium, where for the first time chlorine gas was used as chemical warfare). In the US, chlorination of water began in 1908 in Jersey City, N.J. and within a few years became a widely practice across the United States [18, 19]. At that time, there was no concern about the possible health risks of chlorine used as disinfectant. Trichloramine was even used for bleaching wheat flour in the so-called "agene process" that was in application for most of the first 50 years of the 20th century in the United States and the United Kingdom. This process was discontinued in the 1950s when it was found that the "agenized" flour was responsible for various neurological disorders in dogs as a result of the conversion of methionine into the neurotoxic amino acid methionine sulfoximine [20, 21].

If one excludes occupational or accidental exposures, till the midst of the 20th century, human exposure to CPs in industrialized countries was mainly by the oral route essentially through the consumption of drinking water or of foods cleaned or cooked with chlorinated water. There was probably some exposure by skin absorption when bathing or showering but only for a very small part of the population since bathrooms were not as common as they are now. However, from the 1960s, with the development of public swimming pools and similar aquatic environments, the pattern of human exposure to CPs in the developed world progressively shifted to inhalation and skin absorption as main routes of exposure. Even if there were already some indoor swimming pools in the main European or US cities in the beginning of the 20th century, the vast majority of public pools that exist now in industrialized countries were built after the 1960s. It is noteworthy that this increasing exposure concerned mainly children who were increasingly taken to swimming pools, first as part of the school curriculum and then as a recreational activity now being offered from their youngest age. This increasing attendance of swimming pools by children has in turn led to substantial changes in the swimming pool environment such as higher water temperatures, increased bathing loads and installation of recreational equipments. All these changes have undoubtedly contributed to raise the levels of CPs in pool air, especially as, at the same time, energy conservation programs reducing ventilation were implemented to face the rising cost of energy. In addition, as traditional pools evolved into leisure pools, they offered more time to children and their families for swimming, playing and relaxing [22].

Outdoor pools have also become very popular over the last decades particularly in wealthy countries with a warm climate. These places have further contributed to increase human exposure to CPs as they offer almost unlimited possibilities of swimming or refreshing during summertime. Most backyards pools are disinfected with chlorine added to water as tablets or sometimes produced *in situ* by the electrolysis of sodium

chloride. Since backyard pools are usually outdoors, they have at their surface virtually no trichloramine owing to their natural ventilation. Outdoor pools, however, have usually much higher levels of active chlorine in water compared to indoor pools. Part of this active chlorine (hypochlorous/hypochlorite) can be transformed into chlorine gas or other irritating volatile by-products that being heavier than air accumulate at the surface of water giving rise to the chlorine smell felt by swimmers. The air just above the surface of backyard pools can also be contaminated by microaerosols containing active and combined chlorine, especially when the pool has high sides limiting ventilation or in the evening or morning when a mist covers the water surface [22].

LEVELS OF EXPOSURE

Fig. (1) shows the major chlorine-based oxidants in the water or air of chlorinated recreational environments such as swimming pools, whirlpools or hot tubes. The concentrations of these oxidants above water surface greatly fluctuate depending on a number of physicochemical variables related to the chlorine dosing, bathing load, mode of swimming, air temperature, ventilation of the hall or aerosols spraying by recreational equipments (cannons, jets and waterfalls). The most powerful and concentrated oxidants in these environments are trichloramine in the gaseous phase and the hypochlorous acid and mono- and dichloramine in the aerosols. The survey of air quality of indoor swimming pools has started only recently and in a few European countries only (e.g. France, Belgium, Germany and Netherlands). Mean levels of trichloramine in the air of public indoor pools were found to vary between 300 and 500 $\mu\text{g}/\text{m}^3$ with extreme values attaining 2,000 $\mu\text{g}/\text{m}^3$ (concentrations averaged over a period of two hours and measured at a height of 1.5 m) [13, 23-26]. Trichloramine gas appears thus as one of the most concentrated air pollutants to

which children of industrialized countries are regularly exposed (mean concentrations of other indoor or outdoor air pollutants in Europe seldom exceed 300 $\mu\text{g}/\text{m}^3$) [27]. However, just above the water surface, pool air contains a number of other CPs such as chlorine gas and chlorinated microaerosols that also contribute to the burden of oxidants inhaled by swimmers. The only study that attempted to assess the levels of these other oxidants at the surface of swimming pools is that Drobnick *et al.* [28]. Studying the air at the surface of different pools, these authors obtained a mean concentration of 420 $\mu\text{g}/\text{m}^3$ for chlorine gas. This study, however, provided no evidence indicating that their measurements were specific of chlorine gas and free of interference by trichloramine or chlorinated aerosols.

Swimmers and especially competitive swimmers training intensively in indoor chlorinated pools represent one of the populations the most exposed to CPs. Swimmers are mainly exposed to CPs when actively inhaling air and aerosols floating just at the surface of the water. When the pulmonary ventilation level exceeds about 30 l/min, there is a shift from nose breathing to combined mouth and nasal breathing, allowing water-soluble gases and aerosols to by-pass the nasopharynx filter and thus to penetrate more deeply in the lung. A swimmer training intensively for 30 hours per week is exposed to these CPs 20 times more than a lifeguard working in the same pool and 100 times more than a recreational swimmer [29,30].

Among recreational swimmers, exposure to CPs culminates in young children who probably are also the most vulnerable to these chemicals. Because most children cannot really swim before the age of 6 or 7 years, they have to attend the small pool, which is shallow, hot and usually more polluted than the large pool. For instance, concentrations of trichloramine in the air around the small pool are on average 50% higher than that observed on the side of the large pool. In addition, when children play or learn to swim, they inhale and swallow more aerosols and water droplets containing hypochlorous acid and

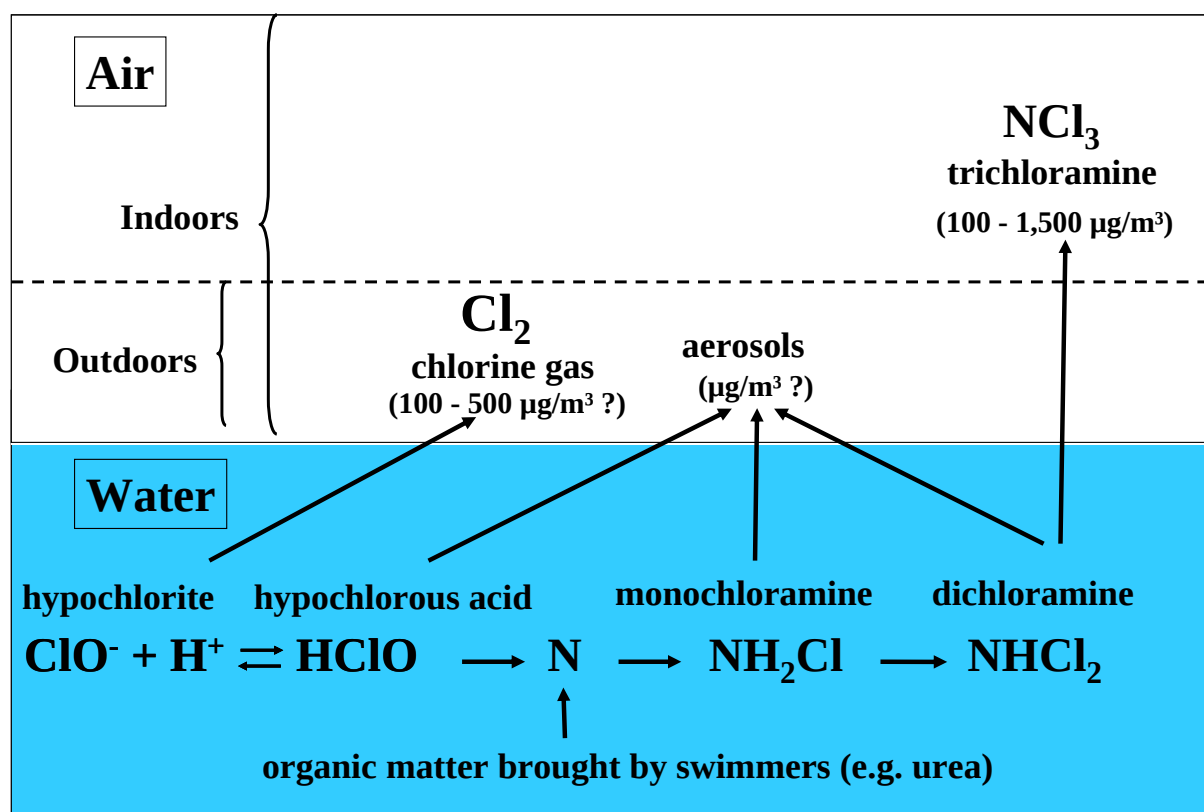


Fig. (1). Major chlorine-based oxidants present in the water and air of indoor or outdoor chlorinated swimming pools and of similar aquatic environments.

soluble chloramines. These can be carried more or less deeply into the respiratory tract depending on the size of aerosols and the respiration pattern (oral vs. nasal breathing) [29,30]. Because of their greater surface area-to-body mass ratio, children also absorb more water-soluble CPs (e.g. chloroform and other trihalomethanes) across their skin in proportion to their body weight.

ALLERGIC DISEASES ASSOCIATED WITH EXPOSURE TO CHLORINATION PRODUCTS: CASE REPORTS

Since the introduction of the chlorination process, case reports have sporadically appeared relating the development or worsening of local or systemic allergic diseases to the irritating effects of CPs. Allergic reactions involving the skin were described as early as in 1930s in French workers exposed to sodium hypochlorite bleach [31-33]. In these early reports, it was already noted that a local epicutaneous or intradermal testing could produce systemic skin eruptions effects with, in extreme cases, anaphylactic reactions. Cases of skin reaction due to repeated or excessive exposure to hypochlorite have been described as allergic contact dermatitis (delayed type hypersensitivity) [34]. A few reports have described an immediate type hypersensitivity reaction resulting in an immunological contact urticaria upon contact with hypochlorite containing cleaning agent [35] and chlorinated swimming pool water [36, 37].

There have been also several reports of asthma induction or exacerbation by the inhalation of CPs emanating from drinking or recreational water. The first case was described in 1934 by Watson and Kibler [38] for a patient who developed gastrointestinal disturbances and bronchial wheezing every time he drank from the municipal water supplier. In 1995, Fjellbirkelan *et al.* [39] described symptoms of exercise-induced asthma in four young athletes training intensively in an indoor chlorinated pool. Three of them had no history of asthma and started to develop the symptoms after several years of training while in the fourth one, who had childhood asthma, asthma symptoms were aggravated by swimming. The four swimmers complained more of symptoms when the air was warm or when there was a strong chlorine smell, leading the authors to suspect the presence of irritating substances in the pool air. More recently, Thickett *et al.* [11] described a series of three workers, two lifeguards and one swimming instructor, who developed occupational asthma following exposure to airborne chloramines in three different indoor swimming pools disinfected with sodium hypochlorite. Air measurement in one of these pools showed trichloramine levels in the range of 100 to 570 $\mu\text{g}/\text{m}^3$. The first asthma symptoms occurred after 10 to 15 years of exposure. The three workers had immediate asthmatic reaction (decreased peak expiratory flow) after challenge with trichloramine (concentration around 500 $\mu\text{g}/\text{m}^3$) or swimming pool air (one worker). Two of the workers were atopic, one with a positive reaction to house dust mite and grass pollen and the other to house dust mite, cat dander and moulds. The second case report, published in 2003 by Goverdham and Gaston [40], is also interesting because it involves sodium dichloroisocyanurate, the stabilized form of chlorine used in most backyards pools. These authors described three cases of dermatologists who developed fingertip dermatitis following contact with Sanichlor® (sodium dichloroisocyanurate) used for the disinfection of tonometers. One of the dermatologists progressively developed generalized urticaria followed by angioedema of the lips. After seven years, this dermatologist noticed increasing breathing problems that coincided with her work in the operations room and remitted at weekends and holidays. She was diagnosed with late-onset asthma with severe nocturnal dyspnoea. Her general health improved when

Sanichlor® was replaced with hydrogen peroxide and there were also no complaints of dermatitis among the staff.

EPIDEMIOLOGICAL STUDIES ON THE RISKS OF RESPIRATORY OR ALLERGIC DISEASES ASSOCIATED WITH CHLORINATION PRODUCTS

Competitive Swimmers

The existence of respiratory and allergic problems in competitive swimmers has been known for more than two decades. They received very little attention from the scientific and medical communities who attributed them to a selection bias because swimming in the hot and humid air of an indoor pool is a well-tolerated exercise by asthmatics [22]. One of the first studies documenting the higher prevalence of allergic diseases in competitive swimmers is that of Zwick *et al.* in 1990 [41] who compared the occurrence of atopy and bronchial hyperresponsiveness (BHR) to metacholine between 14 competitive swimmers and 14 age- and sex-matched controls. Both sensitization to aeroallergens and increased BHR were found to be more prevalent in swimmers (in 11 out of 14 for both tests) than in controls (in 5 and 4 out of 14, respectively). A similar observation was made by Potts [42] when he compared a group of 35 competitive swimmers with 17 non-swimming athletes. Over 60% of the competitive athletes had a positive BHR to metacholine test against only 1.5 % in controls. Potts [42] also reported the results of a questionnaire-based survey of respiratory problems in 738 competitive swimmers. Among respiratory illnesses, bronchitis (24.9 %), hay fever (16.9 %), asthma (13.4 %) and pneumonia (10.2 %) were frequently reported. The swimmers were also suffering from a number of physician-diagnosed allergies, among which the most frequent were allergy to dust mite (20.9%), pollen (19.2%), animal dander (17.1%), grasses (17.1%) and moulds (8.5%). A total of 544 swimmers, i.e. 73.8% of the participants, reported smelling a strong chemical odor in the swimming pool at one time or another and they associated many of the respiratory symptoms (e.g. coughing, wheezing, chest tightness) with this strong chemical odor. In a study involving 42 elite swimmers, Helenius *et al.* [43] found that 50% of them were atopic (at least one positive skin prick test), 36% had an increased BHR to histamine and 29% had hay fever. Total asthma defined as current asthma (positive BHR test and EIB symptoms) was found in 12 swimmers (29%), representing thus a six-fold increase as compared to controls. When swimming and atopy were combined, the risk of asthma was 96 times higher than in non-atopic non-swimmers. Helenius *et al.* [44] conducted a five years follow-up study of 26 elite swimmers who ceased training and 16 who continued training. In swimmers who stopped high-level training, BHR and asthma attenuated or even disappeared while airways inflammation (eosinophils in sputum) did not change significantly. In highly trained swimmers who remained active during the follow up, the three indicators persisted and even tended to be aggravated. The reversibility of asthma and airways inflammation after cessation of swimming is an important finding since this refutes the widespread claim that the higher asthma prevalence in elite swimmers is due to a selection bias. This conclusion is supported by the study of Varraso *et al.* [45] who examined the relationships between blood markers of oxidative stress and training or trichloramine exposure in twenty-two adult swimmers. The activities of $\text{Cu}^{2+}/\text{Zn}^{2+}$ erythrocyte superoxide dismutase and of plasma glutathione peroxidase were found to increase with exposure to trichloramine independently of the effects of training. If as suggested by these studies, irritating effects of CPs contribute to the respiratory problems of swimmers, the mechanical stress imposed on the lung epithelium by the intense training could also play a role in these problems [9, 10].

Recreational Swimmers

Case reports regularly appear describing cases of lung injury in recreational swimmers and other pool attendees accidentally exposed to chlorine gas in indoor swimming pools [46-52]. Fortunately, lung damage observed in these circumstances is usually transient with a complete recovery of the lung function after a period of a few weeks. The possibility, however, that the chlorine-laden atmosphere of indoor swimming pools can cause chronic effects on the lungs of recreational swimmers appeared only recently when new non-invasive tests of lung damage were applied for the first time to children [9]. In a cross-sectional study primarily designed to assess the chronic effects of air pollution on the respiratory tract of schoolchildren, Bernard *et al.* [13, 53] unexpectedly found that the main factor damaging the lung epithelium barrier was the regular attendance of an indoor chlorinated pool. The serum concentrations of the surfactant-associated proteins A and B increased in a dose-dependent manner with the cumulated time the children had spent with school in an indoor chlorinated pool. In a retrospective analysis of asthma prevalence data among 1811 schoolchildren in Brussels, Bernard *et al.* [13] found that the prevalence of asthma in these children was strongly associated with their cumulative pool attendance (CPA) at school, a compulsory activity in Belgium. Associations between childhood asthma and CPA were the strongest when pool attendance was cumulated from birth till the first grade of primary school (Fig. 2). Adjusting the CPA for the pool height, a surrogate indicator of the pool air quality, strengthened these associations. They were also reinforced by adjustment for the exposure to tobacco smoke and pets, two variables that appeared to act synergistically with pool attendance. This early study was welcome with much skepticism

and criticized by some authors arguing that the strength of associations had been overestimated due to data aggregation [54], a criticism that the authors of the Belgian study refuted [55]. These early observations, however, were confirmed in a subsequent cross-sectional study where the relationships between childhood asthma, atopy and CPA were explored using objective outcome measures [14]. This study, also conducted in Brussels, involved a total of 341 schoolchildren aged 10-13 years who had attended at a variable rate the same public pool (trichloramine in air: 300-540 $\mu\text{g}/\text{m}^3$). Children examination included a questionnaire, an exercise-induced bronchoconstriction test (EIB test), the measurement of exhaled NO (eNO) and of total and aeroallergen-specific serum IgE. CPA by children (range: 0-1818 hrs) emerged among the most consistent predictors of asthma (doctor-diagnosed or screened with the EIB test) and of elevated eNO immediately after atopy and family history of asthma or hay fever. Whereas the risk of elevated eNO increased with CPA independently of total or specific serum IgE, the probability of developing asthma increased with CPA only in children with serum IgE > 100 kU/l (Fig. 2). These associations between pool attendance and risk of asthma or elevated eNO were not biased by the possibility that children with a medical diagnosis of asthma or from asthmatic parents could be led to attend swimming pools more frequently than other children (reverse causation). CPs contaminating the air and water of indoor pools appear thus to act as adjuvant promoting the development of asthma in atopic children, especially in young children attending the small heavily polluted pool. A recent study in Germany has provided further evidence suggesting that swimming pool attendance during infancy might contribute to the development of allergic diseases. By retrospectively collecting information on swimming pool attendance and medical history in a cohort of

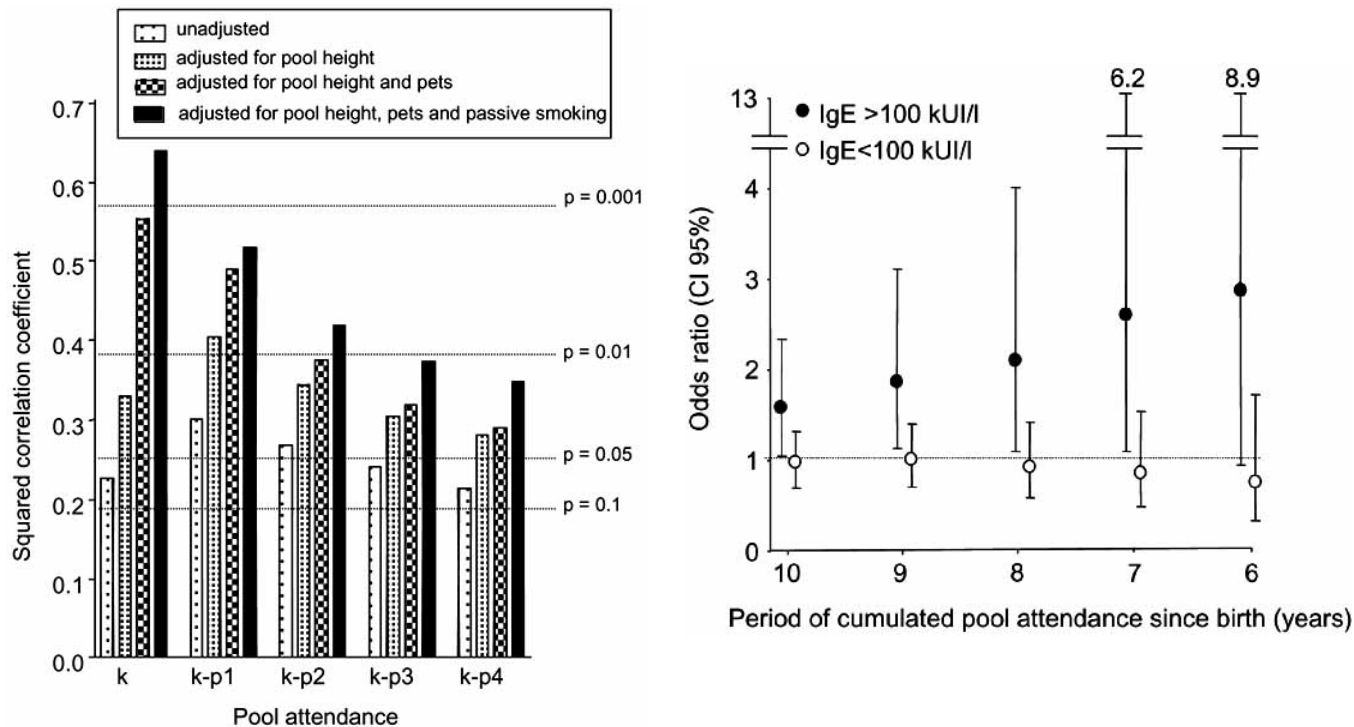


Fig. (2). Effect of timing of exposure on the risk of childhood asthma associated with CPs in swimming pools. The left panel shows the square correlation coefficients between asthma prevalence in 15 primary schools (total 1881 children) in Brussels and the cumulative pool attendance (min/week $\times$ years) calculated for each school over increasing periods of time, from the kindergarten (k) up to the last grade of primary school (p4) [13]. The right panel shows the odds ratios (with 95% confidence interval) for developing asthma in 341 schoolchildren in Brussels according to the pool attendance cumulated over increasing shorter periods of time after birth and the total serum levels of IgE. The odds ratios have been adjusted for the traditional risk factors of asthma [14].

2606 adults aged 35-74 years, Kohlhammer *et al.* [56] found increased risks of hay fever in adults who were exposed to swimming pools at school age (OR 1.74, 95% CI 1.09-2.77), were frequently exposed during the past 12 months (OR 1.32, 95% CI 0.92-1.89) or were ever exposed (OR 1.65, 95% CI 0.98-2.78).

As suggested by studies on recreational swimmers [13,14, 53, 56], one of the most critical factors in determining the risks of CPs for children appears to be the timing of exposure. This unavoidably raises the question of the safety of the baby swimming practice, especially as the higher water temperature and the greater organic pollution in swimming pools attended by young children are conditions favoring the formation of chlorination by-products. The first study to have addressed this issue is that of Nystad *et al.* [57] who found that the baby swimming practice was associated with an increased risk of recurrent respiratory tract infections and otitis media in the first year of life. Dividing the children according to parental atopy (asthma, hay fever or eczema) showed that these risks concerned mainly children from atopic parents (OR 2.08, 95% CI, 1.08 vs. 4.03). This study, however, did not report data on the levels of chlorine in the pools attended by the babies, nor did it assess the effects of baby swimming on the development of asthma and allergy later during childhood. In their cross-sectional study on schoolchildren, Bernard *et al.* [58, 59] made rather similar observations when comparing the respiratory health, allergic status and pulmonary epithelium integrity of children who took part in a baby swimming program with that of their peers who did not. Children who had been swimming baby (n=43) showed a significant decrease of serum Clara cell protein (CC16), a marker of the integrity of Clara cells lining terminal airways. The decrease was even more significant when calculating the serum CC16/SP-D (surfactant-associated protein D) ratio, an index integrating both the damage to Clara cells and the disruption of the lung epithelial barrier. Baby swimming emerged as the only statistically significant predictor of serum CC16 and this practice was the strongest determinant of the CC16/SP-D ratio. These effects were associated with higher risks of asthma (OR 3.0, 95% CI 1.3-7.4) and of recurrent bronchitis (OR 2.6, 95% CI, 1.3-5.1). Passive exposure to tobacco alone had no effect on these outcomes but appeared to interact with baby swimming practice to increase the risks of asthma (parental smoking at home, OR 6.54, 95% CI 1.18 to 36.4) or of recurrent bronchitis (maternal smoking during pregnancy, OR 6.99, 95% CI 1.60 to 30.5) [58, 59]. It should be noted that these findings among recreational swimmers were all based on multivariate analyses adjusting the associations between asthma and swimming pool attendance for other risk factors including atopy, parental asthma, passive smoking or exposure to household chemicals or to chlorine of outdoor backyard pools.

In Italy, Carraro *et al.* [60] recently compared the levels of eNO between children who were regularly attending an indoor swimming pool (n=100) and children who were not (n=141). They found no difference in the mean levels of eNO between the two groups, which is at variance of observations made in Belgium. A possible explanation for this discrepancy is that Carraro *et al.* [60] analyzed their data by classifying children in swimmers and non-swimmers on the basis of their current swimming practice (more than one hour per week during at least the last 6 months) and not on the basis of their attendance of swimming pools during their early childhood, which according to the Belgian studies appears to be the most critical period for the risks of asthma and lung inflammation associated with pool attendance. Carraro *et al.* [60] also did not consider the attendance of open air swimming pools, which in a country like Italy are likely to represent a more important source of exposure to CPs than indoor pools.

Children Living in Places Cleaned with Chlorine Bleach

The use of chlorine bleach for house cleaning appears to exert a protective effect towards the risk of asthma and allergy to indoor allergens [14, 61]. These divergent effects of chlorine when the chemical is used to clean surfaces or to sanitize recreational water are not really inconsistent. Exposure conditions to chlorine are indeed radically different when children live in a house cleaned with bleach compared with when they swim in an indoor chlorinated pool [14, 61]. When a house is cleaned with bleach, children are not likely to be exposed to high concentrations of chlorine gas or trichloramine simply because they are not directly involved in the cleaning tasks. In that situation, the balance for children - but not necessarily for people doing the cleaning - is clearly in favor of the beneficial effects of chlorine that consist in a decreased risk of asthma and respiratory allergy [14, 61, 62] as a result of the inactivation of allergens by the hypochlorite [63, 64]. Because of the high microbial risks, day care centers require a daily infection of surfaces and objects that infants can be in contact with. In most industrialized countries, this daily disinfection is achieved by using chlorine bleach, a practice that might explain the lower levels of indoor allergens (e.g. house-dust mite) in day care centers compared to private houses [65, 66]. This protective effect of day care attendance against the risks of asthma and allergic diseases observed in some studies [67, 68] might thus be a consequence not of the higher risk of infectious diseases but of the efficient removal of allergens achieved when using bleach [61]. The possibility however that chlorine used for house cleaning may adversely affect the respiratory tract of children can not be definitively ruled out. There is indeed some evidence that irritating gases released from bleach might persist in home and, alone or in interaction with other factors such as tobacco smoke, could increase the risk of respiratory symptoms or recurrent bronchitis during early childhood [61, 69].

Lifeguards and Pool Workers

The first study that specifically addressed the respiratory risks of occupational exposure to trichloramine was that the Massin *et al.* [25] who conducted a survey on a total of 334 lifeguards working in 46 public swimming pools (n=228) and in 17 leisure centers. This study provided the first large series of trichloramine concentrations in the air of indoor swimming pools by measuring this gas on a total of 1262 air samples. Trichloramine concentrations were found to be greater in leisure pools (mean 670 $\mu\text{g}/\text{m}^3$, SD, 170 $\mu\text{g}/\text{m}^3$) than in public pools (mean 240 $\mu\text{g}/\text{m}^3$; SD, 370 $\mu\text{g}/\text{m}^3$), a difference that the authors attributed to the higher temperature and water turbulence in leisure pools (toboggans, waves...). Respiratory symptoms were recorded by a self-administered questionnaire and BHR was screened using the metacholine test. The prevalences of eye, nose and throat irritation symptoms were increased and correlated with both the trichloramine levels in pool air and the cumulative exposure to trichloramine. The BHR test was positive in 28.2 % (22/78) of female lifeguards, a prevalence that surprisingly was the double of that observed in male lifeguards (13.7 %, 35/256). Prevalences of BHR were not related to the cumulative exposure but it should be noted that the dose-response analyses across cumulative exposure categories did not consider the possibility of interaction with atopic status that was noted in studies on swimmers [14, 44]. In addition, as acknowledged by the authors, it is likely that the dose-response analysis has been confounded by a selection bias due to the healthy worker effect. This bias might explain why the prevalence of asthma (only 2.4 %) in this population exposed to lung irritants was lower than in the general population (around 4 % in the adult French general population). More recently, in the Netherlands, Jacobs *et al.* [26] conducted a

rather similar survey in order to assess the relationships between swimming pool characteristics and respiratory symptoms in employees. Questionnaires were available from 624 pool workers from 38 swimming facilities. General respiratory symptoms including symptoms indicative of asthma, were significantly elevated in pool workers compared to the general Dutch population (OR ranging from 1.4 to 7.2). Interestingly, upper respiratory symptoms were significantly associated with cumulative chloramine levels (OR>1.4 for hoarseness, lost voice, sinusitis). An aggravation of existing respiratory diseases or interactions between irritants and allergen exposures were proposed to explain these associations.

Workers in the Food Industry

The use of chlorine as disinfectant or cleaning agent in the food industry can generate atmospheres that are rather comparable to that of indoor swimming pools. In that respect, Hery *et al.* [70] carried out in the late 1990s a pioneer study by examining workers of a green salad plant who were complaining of eye and upper respiratory tract irritation. These authors showed that the irritating effects felt by the workers were caused by trichloramine and water-soluble chloramines released in the air of the facility when salad was cut and washed with a hypochlorite solution. The exposure of workers to chloramines measured with personal samplers ranged from 200 to 5,000 $\mu\text{g}/\text{m}^3$. Similar findings were reported by the US centers for diseases control and prevention (CDC) and the US national institute for occupational safety and health (NIOSH) when investigating the cause of the complaints of eye and respiratory tract irritation among workers of a poultry processing facility [71]. Again, the complaints were found to be associated with higher concentrations of trichloramine and water-soluble chloramines in the air. There were significant associations between the mean concentrations of trichloramine and the cross-shift declines in lung function. By applying the same protocol as in their study on lifeguards [25], Massin *et al.* [72] have assessed respiratory symptoms, BHR and exposure to trichloramine and aldehydes among 175 workers doing cleaning and disinfecting tasks in the food industry. Although eye and respiratory symptoms were associated with both the levels and the duration of exposure to trichloramine, no exposure-effect relationship emerged with BHR, a finding that is reminiscent of that made in lifeguards [25]. However, the study of Massin *et al.* [72] like other studies on pool and cleaning workers, did not assess the effects of chloramines on the risks of allergic diseases nor did these studies adjust their observations for the atopic status of workers or else consider the possibility that chloramines could interact with atopic status to promote the development of asthma.

Industrial Workers

Chlorine gas is a widely used industrial chemical and it is known for more than a century that accidental release of this gas can cause severe lung injuries and even death among industrial workers [73-75]. Depending on the inhaled dose, chlorine gas produces a wide spectrum of acute effects ranging from an upper airways irritation to bronchitis, pneumonitis and even a fatal oedema. Some people can develop a form of persistent non-immunological asthma called reactive airways dysfunction syndrome [76]. A similar syndrome affecting the upper airways (RUDS) has also been defined to describe the chronic rhinitis associated with episodes of acute exposure to chlorine [77]. Industrial workers repeatedly exposed to peaks of chlorine gas are at higher risk of developing asthma or a persisting airflow limitation [78, 79]. Interestingly, gassings accidents involving chlorine in pulp mill workers have been shown to be associated with an increased concentration of nitric oxide in exhaled air

(eNO), suggesting that a chronic lung inflammation has been triggered by these acute exposure episodes [80].

Domestic Cleaners

Accidental exposures to chlorine gas are also regularly described following the misuse of chlorine bleach by domestic cleaners [81, 82]. Medina-Ramon *et al.* [83] compared the occupational exposure history of 160 domestic cleaning women with asthma symptoms and 386 without respiratory symptoms. Lung function tests, metacholine challenge and serum IgE testing were performed. Asthma symptoms were related to chlorine exposure that was detectable in air during the cleaning with bleach. Atopy defined as specific serum IgE greater than 0.35 kUI/l for at least one allergen was not different between cases and controls (15 vs. 16 %) but intriguingly the proportion of women with elevated total serum IgE (>100 kUI/l) was four times greater in cleaners (27%) than in controls (6%), suggesting that the cleaning operations had increased the risk of allergic sensitization.

Ecological Studies

A few ecological studies have explored the associations between the prevalences of atopic diseases in children and their exposure to chlorine in drinking or recreational water. In a study involving 458,284 children, aged 6-12 years, in 1016 public elementary schools in Japan, Miyake *et al.* [84] found a statistically significant and slightly J-shaped relationship between the chlorine content of the water supply and the prevalence of atopic dermatitis. A similar association was found in a previous study in the United Kingdom but it did not persist after adjustment for confounders [85]. Using the data of the ISAAC study, Nickmilder and Bernard [86] found that the prevalence of childhood asthma and the number of indoor chlorinated swimming pools in Europe were linked through associations that were geographically consistent and independent of the climate, altitude and the socio-economic status of the country. The strongest associations were found with ever-diagnosed asthma that was also the asthma indicator showing the strongest East-West gradient across Europe. These ecological studies are of course not exempt from the risks of bias and misclassification inherent to any ecological study. However, when evaluating the causality of associations emerging between asthma and swimming pool accessibility in Europe according to the Hill's criteria (strength and consistency of associations, biological plausibility, temporality,...), Nickmilder and Bernard [86] concluded that it would not be reasonable to dismiss these associations as arising from bias or lack of adjustment. Concerning for instance biological plausibility, these authors pointed out that engineers know for a long time that the atmosphere of indoor swimming pools is one of the most aggressive to be found in building environment. The discovery that this chlorine-laden atmosphere can be deleterious to the lungs of young children exercising in it is thus nothing surprising.

EXPERIMENTAL STUDIES

In Vitro Studies

Hypochlorous acid and chloramines are molecules of particular interest for immunologists and cell biologists. These chlorine-based oxidants are indeed produced by inflammatory cells possessing a myeloperoxidase activity that release them to fight infections or to facilitate cell recruitment. Studies on cell cultures and isolated organs have shown that these chemicals are powerful membrane penetrating oxidants that react rapidly with the sulfhydryl groups of proteins of the cytoskeleton and

extracellular matrix, thereby causing cell retraction, disruption of cellular junctions and an almost immediate increase of endothelial or epithelial permeability [2-4]. For instance, hypochlorous acid can cause an immediate increase of the microvascular permeability of isolated rat lung [3] and of the permeability of the rabbit tracheal epithelium [87]. Monochloramine can disrupt the tight junctions of human colonic Caco-2 epithelial monolayers and thus compromise the function of the epithelial barrier of the intestine [88]. Hypochlorous acid produced by neutrophils also reacts with endogenous amines to produce less toxic and more long-lived chloramines that may affect the functions of the immune system cells and in particular of the antigen-presenting cells (dendritic cells) [89]. All these effects are induced by relatively low concentrations of hypochlorous acid or monochloramine without any apparent structural damage to the cells.

Animal Studies

There have been relatively few animal studies of the long-term toxic effects of CPs. In most of these studies, the animals were exposed via drinking water and the observed effects were usually considered as mild and of little relevance to human exposure because of the high doses required for inducing them. The effects of chlorine-based oxidants by inhalation or skin contact have received even less attention with the exception of the chlorine gas. Exposure of rodents to high concentrations of chlorine gas has been shown to cause oxidative injury to airways with epithelial loss, an increased BHR to metacholine and an increased production of nitric oxide production, all changes that are reminiscent of those observed in humans [90]. Although chloramines and hypochlorite are recognized as potent lung irritants when inhaled as gases or aerosols, animal data regarding the acute or chronic inhalation toxicity of these chemicals are very limited, too. Gagnaire *et al.* [91] showed that trichloramine has the same irritating potency as chlorine and formaldehyde while Barbee *et al.* [92] demonstrated that it causes fatal lung oedema at very high doses. The first experimental study that really examined the pulmonary effects of this gas at relatively low concentrations is that of Carbonnelle *et al.* [10]. Mice were exposed to trichloramine at the concentration of 11.9 mg/m³ for 1, 2 or 8 hours. After 4 hours of exposure, mice showed a time-dependent elevation of serum CC16 that was paralleled by a decrease of the protein concentration in lung lavage. After 8 hours of exposure, these changes were accompanied by an elevation of both albumin and total protein in bronchoalveolar lavage fluid. The level of LDH in bronchoalveolar lavage fluid and the histological examination did not reveal any overt cytotoxicity. Mice acutely exposed to trichloramine showed thus an increased bidirectional leakage of proteins across the pulmonary epithelium. These effects were not found at lower concentrations of trichloramine that were also tested in this study (3.45, 0.8 and 0.53 mg/m³). To the best of our knowledge, the effects of aerosolized hypochlorous and chloramines on the respiratory tract have never been studied in experimental animals.

Studies on Human Volunteers

Studies on exercising healthy volunteers with-short term exposure to low concentrations of chlorine gas have shown that from a concentration of 1 ppm chlorine gas produces a significant decrease in expiratory flows and lung capacity volumes, an increase in airway resistance as well as inflammatory changes in the nasal cavity [93]. The no-effect level for these effects was estimated at 0.5 ppm. Subjects with pre-existing BHR appear, however, more sensitive to the irritant effects of chlorine. These subjects can experience significant

decreases in air flow and increases in airways resistance already from chlorine gas concentrations of 0.4 ppm [94]. Irritant effects of chlorine gas on the nasal mucosa are also more pronounced in subjects with seasonal allergic rhinitis (hay fever) than in nonrhinitic subjects [95]. Because of the difficulties to conduct inhalation studies under well-controlled conditions, the short-term effects of trichloramine in healthy volunteers were so far studied only by exposing them to the atmosphere of indoor chlorinated swimming pools. Using serum pneumoproteins as markers of lung epithelium damage, Carbonnelle *et al.* [10] and Bernard *et al.* [13] have shown that trichloramine can cause a transient disruption of the deep lung epithelium, already after a one-hour-exposure to a concentration of 540 µg/m³. The no-effect level for these permeability changes might be around 300 µg/m³ since swimmers training intensively in an atmosphere containing 340 µg/m³ of trichloramine showed only minimal changes in the serum levels of pneumoproteins [10]. Swimming in the warm and humid air of an indoor pool is regarded as a beneficial sport for asthmatics. Most physicians and medical associations recommend thus swimming in indoor pools to asthmatics, a recommendation that sounds paradoxical giving the well-known sensitivity of the airways of asthmatics to irritants. A few physicians have tried to draw the attention of the medical community to the possible adverse effects of pool chlorine for asthmatics [96, 97]. The deeply rooted belief that swimming pool environment is safe for asthmatics has again been questioned by a recent study showing that the BHR to metacholine in asthmatics was significantly increased after only a 12-minutes immersion in a chlorinated whirlpool bath [98]. Although this study did not measure chlorine in the air above the whirlpool, there is little doubt that this increased BHR is due to the irritating effects of chlorine gas or chlorinated aerosols. This conclusion is also supported by the study of Boulet *et al.* [99] who compared the airways inflammation induced by high intensity training between swimmers and runners, with hyperresponsive or with normoresponsive airways to metacholine. While airways inflammation evaluated on the basis of neutrophils in induced sputum was found in all groups, the inflammatory response was statistically significant only in swimmers with BHR, meaning that this group was more sensitive.

MECHANISMS BY WHICH CHLORINATION PRODUCTS COULD INDUCE ALLERGIC DISEASES

In allergic sensitization, allergens must cross epithelial barriers to interact with antigen-presenting cells (dendritic cells). Tight junctions occluding the paracellular routes are the main barriers preventing this penetration of allergens. The way these efficient barriers are disrupted to allow the delivery of allergens is still poorly understood. Evidence from recent *in vitro* studies suggests that because of their proteolytic activity some allergens (the house dust mite Derp 1 and Derp 2 allergens and the *Penicillium* and *Aspergillus* Pen ch 13 allergens) can facilitate their passage by opening the tight junctions but it is unknown to what extent this phenomenon effectively occurs *in vivo* [100-103]. It has also been speculated that viral infections could play a role by damaging the airways epithelium. Evidence from *in vitro* and *in vivo* studies reviewed here indicates that the acute or chronic epithelial hyperpermeability induced by CPs might constitute another mechanism by which allergens could have access to the dendritic cells. Chlorine-based oxidants in water and air could thus play the role of chemical adjuvant facilitating the transepithelial passage of allergens and thereby amplifying the sensitization in atopic subjects. This mechanism could explain the pool chlorine/atopy interaction in the development of childhood asthma [14] and the increased risk of allergic diseases observed in recreational or elite swimmers [13,

14, 41-44, 56]. The role of epithelial hyperpermeability in the development of sensitization is also suggested by experimental studies on monkeys demonstrating that ozone - an oxidant also disrupting the lung epithelial barrier [104] - promotes the atopic sensitization to platinum or house dust mite allergen [105, 106]. Following excessive or repeated exposures, CPs have also been found to damage the epithelial cells. Consequences of this damage can be manifold since epithelial cells are known to synthesize and secrete a number of molecules regulating allergic or inflammatory responses such as cytokines/chemokines, growth factors, lipid mediators or anti-oxidant/inflammatory proteins [107]. This decreased secretion by adding to the intravascular leakage of proteins across the disrupted epithelial barrier, contributes to further reduce the intrapulmonary pools of these secretory products. An example is the reduced secretion of the anti-inflammatory CC16 that has been found in children having regularly attended indoor swimming during their early childhood [58, 59, 108].

Hypochlorous acid and chloramines can also react with proteins, breaking the tolerance of self-proteins or increasing the immunogenicity of non-self proteins by creating new epitopes or revealing cryptic epitopes through protein unfolding [109-111]. In some circumstances, however, the opposite can be observed. Chlorine-based oxidants can indeed sufficiently denature or fragment proteins to completely abolish their immunogenicity. The cat (Fed1) and house dust mite (Der p1) allergens, for instance, have been found to be inactivated by low concentrations of chlorine bleach [63, 64].

Fig. (3) illustrates how chlorine-based oxidants in water or air could disrupt epithelial barriers and thereby facilitate the entry of allergens and their delivery to immunocompetent cells. The affected organs will be different depending on the water solubility of these chemicals and on whether they are present in air as gases or aerosols. Trichloramine would be particularly active in inducing such a mechanism in the deep lung. Because of its water insolubility, trichloramine gas is indeed toxic to distal airways [9, 10, 108], which are precisely the major sites of inflammation and airflow restriction in asthma [112]. By contrast, hypochlorite, chloramines and other non volatile CPs when inhaled as aerosols or when entering with water in the nasal cavity would disrupt the epithelial barrier of upper airways, making them more permeable to allergens. Permeability changes induced by chlorine gassing off at the surface of chlorinated water should predominantly affect the upper airways since at relatively low concentrations as found in the air above swimming pools (<2.5 ppm) more than 90% of this water-soluble gas is absorbed in the nose during nasal breathing [113].

Even though CPs probably represent the strongest triggers of the above mechanisms because of their strong oxidizing potential and their high concentrations in recreational environments, other stressors have the potential to cause similar epithelial effects and thus to act additively or synergistically with CPs. Ambient air pollutants (such as ozone or diesel exhaust particles), tobacco smoke, endotoxins, dry or cold air, or strenuous exercise are all factors that could compromise the epithelial barriers of the respiratory tract and

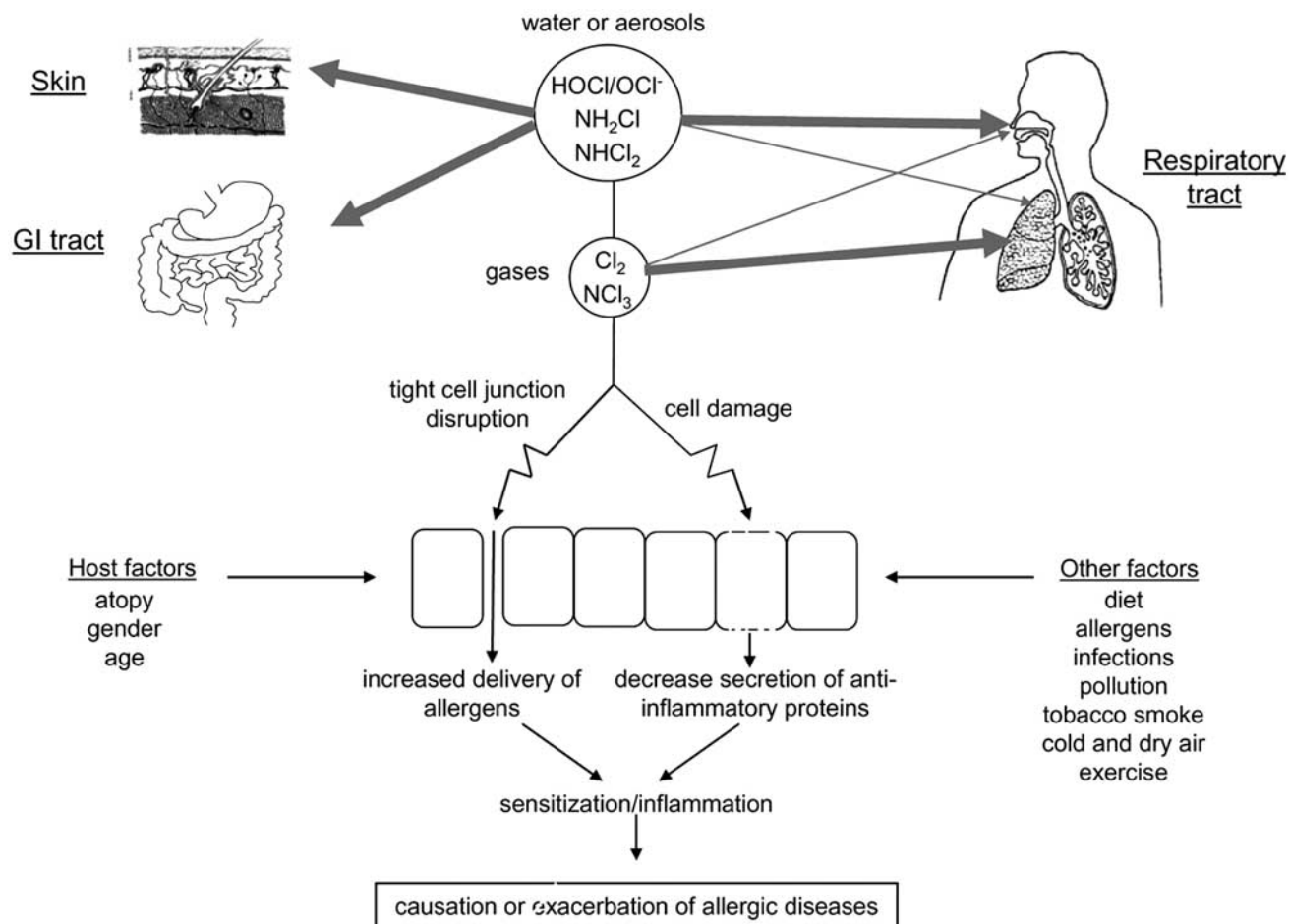


Fig. (3). Scheme illustrating how chlorine-based oxidants in water or air can disrupt the epithelial barriers of exposed organs and thereby facilitate the penetration of allergens and the allergic sensitization.

thereby also facilitate the penetration of allergens and thus the allergic sensibilization [114].

THE CHLORINE VERSUS THE HYGIENE HYPOTHESIS

Over the last three decades, the prevalence of allergic diseases such as atopic asthma and eczema has dramatically increased in the developed world [115-117]. In most industrialized countries, asthma has become the most common chronic childhood disease. Intriguingly, countries the most affected by this rise are English speaking countries such as the UK, Ireland, Australia and New Zealand where prevalence rates of childhood asthma are up to 10-fold higher than in most Southern and Eastern countries [115-118].

The factors causally driving both the rise and the international variations in allergic disease prevalence are largely unknown. Although genetic factors are important, it is unlikely that they can account for such a rapid increase of all forms of atopic diseases, worldwide. This has led to the suggestion that the rising prevalence of these diseases must be linked to some changes in our lifestyle or environment. Currently, the hypothesis generating the most interest is the "hygiene hypothesis" postulating that the rise in asthma and allergy is due to the decreased exposure to microbiological products and/or infectious agents, especially in early life [119]. Several studies, indeed, have shown a reduced risk of asthma, allergic rhinitis or atopic sensitization in situations with a presumably higher exposure to infectious agents such as large families, day care attendance and exposure to pets or farm animals [119-121]. This protective effect of infection, however, has not been confirmed by other studies [122-124] while some features of the childhood asthma epidemic remain unexplained by the hygiene hypothesis. For instance, asthma has also increased among inner-city children who live in very poor housing conditions presumably somewhat dirty [125]. The hygiene hypothesis is also temporally inconsistent with the rise of childhood asthma, which indeed started after the 1960s whereas major hygienic progresses in industrialized countries were achieved well before the 1940s [126]. To account for these conflicting results, researchers in the fields of epidemiology and immunology regularly reformulate the hygiene hypothesis. After having initially attributed the protective effect to overt viral and bacterial infections, the protagonists of the hygiene hypothesis have linked the protective effect to the exposures to some microbial compounds or postulated the existence of narrow windows of opportunity during early life. Other supporters of this hypothesis invoke the existence of a complex interplay between the immune responses of the host, the characteristics of the invading microorganism, the level and variety of the environmental exposure, and the interactions of all these factors with the genetic background [126, 127].

The recently proposed "chlorine" hypothesis suggests that the link between hygiene and allergic diseases would lie less in the decreasing exposure to microbiological agents than in the increasing exposure of the population to the products of chlorination, the most widely used method to achieve hygiene in industrialized countries. As long as chlorine was mainly used to disinfect drinking water or surfaces, human exposure to CPs was limited to the oral route with a minimal exposure *via* the skin or the respiratory tract. On the contrary, when used for surface disinfection, chlorine bleach appears to protect towards the risks of asthma and sensitization to indoor allergens, most probably by destroying allergens and harmful microbial agents such as fungal toxins and endotoxins [63, 64]. Actually, it is very likely that CPs and allergic diseases started to be linked after the midst of the 20th century with the development of public and leisure pools and similar aquatic environments.

These public recreational areas require indeed high levels of chlorine to cope with the infection risks and because they are mostly indoors, they are highly polluted by volatile or aerosolized CPs, a situation that has been exacerbated by the rising cost of energy. The chlorine hypothesis is consistent with several features of the childhood asthma epidemic affecting the developed countries. First, pool chlorine appears to act as an adjuvant increasing mainly the risk of atopic asthma, which is the asthma phenotype largely responsible for the asthma rise reportedly observed during the last decades. Second, in most developed countries, prevalence rates of asthma appear to show peak in children aged 6 to 14 years, who are precisely the most frequent attendees of swimming pools. Third, in contrast to the major steps in hygiene progress which were achieved in most industrialized countries before the 40s, human exposure to CPs by inhalation and skin contact is much more recent and coincides with the childhood asthma rise. Fourth, the chlorine hypothesis is also consistent with the geographical variations observed in asthma prevalence. As shown by recent international comparisons, the highest rates of asthma prevalence are found in countries like the UK and Ireland, where swimming is very popular and most swimming pools are indoors. Fifth, the chlorine hypothesis provides an explanation for the lack of correlation between the prevalence of asthma and atopy found across populations worldwide. Indeed, populations characterized by a low prevalence of asthma despite a high prevalence of atopy (Gambia, Ethiopia, rural China), or those with a low prevalence of both asthma and atopy [128], all have living conditions such that regularly sending children to swimming pools is far from being a priority. By contrast, populations with high prevalence rates of asthma (regardless of atopy) all live in countries dominated by the Western lifestyle where chlorinated swimming pools are indeed very common. Sixth, the chlorine hypothesis also offers an attractive explanation to the lower prevalences of allergic diseases in populations having kept a traditional lifestyle such as farmers or children of Steiner schools [129].

At this stage of the research, data are too limited to make any reliable estimate of the possible contribution of CPs exposure to the epidemic of asthma and allergic diseases in the developed world. Observations in cross-sectional studies suggest that in atopic children the asthma risk increases by approximately 1 % for each hour a child spends in an indoor chlorinated pool [14] while associations found in ecological studies indicate that indoor chlorinated pools might contribute for up to 40 or 50% of the childhood asthma prevalence in Western Europe [86]. These figures, however, should be interpreted with caution for they are based on relatively few studies and will have to be revised to account for the attendance at outdoor chlorination pools. However, even if any causative relationship between chlorinated pool attendance and asthma is weak, the large number of children regularly attending swimming pools in the Western world would mean considerable overall diseases burden [130]. Given the increasing popularity of swimming pools, there is an obvious need to assess the effects of CPs on swimming pool attendees, to identify the critical routes and levels of exposure as well to further explore the cellular and molecular mechanisms by which these chemicals could promote allergic sensitization. Another obvious step forward is to minimize the human exposure to these reactive chemicals by implementing appropriate standards and reinforcing air and water quality control in swimming pools and other water recreational areas, especially when they are attended by children.

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