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Chloroanisoles may explain mold odor and represent a major indoor environment problem in Sweden

Abstract Indoor mold odor is associated with adverse health effects, but the microbial volatiles underlying mold odor are poorly described. Here, chloroanisoles were studied as potential key players, being formed by microbial metabolism of chlorophenols in wood preservatives. Using a three-stage approach, we (i) investigated the occurrence of chloroanisoles in buildings with indoor air quality problems, (ii) estimated their frequency in Sweden, and (iii) evaluated the toxicological risk of observed chloroanisole concentrations. Analyses of 499 building materials revealed several chloroanisole congeners in various types of buildings from the 1950s to 1970s. Evaluation of Swedish records from this time period revealed three coinciding factors, namely an unprecedented nationwide building boom, national regulations promoting wood preservatives instead of moisture prevention, and use of chlorophenols in these preservatives. Chlorophenols were banned in 1978, yet analysis of 457 indoor air samples revealed several chloroanisole congeners, but at median air levels generally below 15 ng/m^3. Our toxicological evaluation suggests that these concentrations are not detrimental to human health *per se*, but sufficiently high to cause malodor. Thereby, one may speculate that chloroanisoles in buildings contribute to adverse health effects by evoking odor which, enhanced by belief of the exposure being hazardous, induces stress-related and inflammatory symptoms.

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Practical Implications

Dampness, microbes, and chlorophenols are the three prerequisites for chloroanisole formation, and they all occur in buildings worldwide. Consequently, the malodor caused by chloroanisoles from microbial metabolism of chlorophenols in wood preservatives does most likely degrade indoor air quality in many countries. The malodor may be perceived as mold but does not necessarily indicate major problems with dampness and mold as odor thresholds for chloroanisoles are extremely low.

Introduction

Several recent reviews and meta-analyses report that dampness in buildings is associated with multiple allergic and respiratory effects. The negative impact of building moisture on health is likely due to chemical and microbial emissions from the damp building into indoor air. Various potentially hazardous emission factors have been suggested and investigated, for example, spores, cell fragments, mycotoxins, β-glucans, allergens, and volatile organic compounds (VOCs). However, the specific microbial or chemical factors that can explain the

association between damp buildings and ill-health remain to be identified (Mendell et al., 2011; WHO, 2009).

One type of emission that is clearly associated with indoor air quality (IAQ) problems is mold odor, that is, microbial VOC (MVOC) produced by bacteria, actinobacteria, and fungi. In epidemiologic studies, mold odor is generally accepted as a sufficient indicator of dampness in buildings. Generally, mold odor is considered to reflect hidden mold growth with negative impact on health via co-emission of some, as yet, unidentified adverse factors (Mendell et al., 2011; WHO, 2009). Another possibility is that the mere perception of mold odor may cause adverse health effects in residents. In fact, a major role of olfaction is to act as a chemical warning system by mediating health symptoms under certain conditions to signal potential danger as well as to trigger protective psychological reflexes (Cain, 1988; Engen, 1991; Stevenson, 2010). An example of such a condition is believing that the exposure is hazardous (Dalton, 2012), and the belief in the general population that mold is toxic is indeed very common (Chang and Gershwin, 2005).

So far, the MVOCs that constitute mold odor in epidemiological studies have not been well defined and are rarely measured. This lack of vital information most likely reflects that the odorants generating mold odor perception are complex and variable mixtures of low levels of MVOCs that are problematic to analyze. The combination of complex variable mixtures and analytical difficulties makes it difficult in epidemiologic studies to relate subjective odor intensity to objective measures of MVOCs. For mechanistic studies, it is equally problematic to select MVOCs of public relevance.

In this study, we reason that chloroanisoles (CAs) are relevant MVOCs for both epidemiological and mechanistic studies in relation to adverse health effects in buildings with mold odor due to three key characteristics: They reliably indicate moist in building materials, they are perceived at very low concentrations by human olfaction, and they have a characteristic mold odor with the potential to evoke health worries in sensitive individuals.

In moist conditions, microbes produce various CAs by dechlorination and methylation of pentachlorophenol (PCP) or sodium salts of pentachlorophenolate. Products referred to as PCP were introduced in the 1930s and gained global use as algicides, bactericides, fungicides, herbicides, insecticides, and molluscicides, but with the main use as wood preservatives (WHO, 1987). As PCP was also applied in buildings in many countries (WHO, 1987) and as dampness in buildings is common in many countries, with estimates often ranging from 10 to 50% (WHO, 2009), it is likely that negative effects of CAs that are biogenerated from PCP are of global importance. Thus, our study focusing on CAs should be of interest both concerning the role of mold odor in the indoor air setting and in relation to the global use of PCP.

Only two publications addressing the issue of CAs in problem buildings were identified, (Gunschera et al., 2004, 2005). These studies involve five houses with complaints from residents regarding musty odor and reach the conclusion that *'chloroanisoles are good indicators of possible PCP treatment of wood in frame houses and their detection should initiate investigation on PCP contamination'*. Building investigators in Sweden have employed analyses of CAs in relation to perceived mold odor in air and materials since 1999, and we have recently suggested that negative effects of CAs may be common in this country (Lorentzen et al., 2012, 2014). This provides an interesting setting for studies on both mold odor and PCP in relation to IAQ.

The aims of this study were (i) to determine where in buildings and in which types of buildings CAs occur, their existing levels, and/or congener types in samples of air and materials; (ii) to identify and review domestic records that could help elucidate the origin, scale, and characteristics of IAQ problems linked to CAs; and (iii) to perform a toxicological evaluation of CAs.

Our toxicological evaluation highlights the difficulties associated with assessment of adverse health effects in relation to extremely low levels of chemicals that cause odor 'nuisance', but are not toxic *per se*. We argue that olfactory perception may contribute to adverse health effects reported in damp buildings and discuss the possible underlying psychobiological mechanisms.

Materials and methods

This study was granted free access to company databases and files owned by Eurofins Pegasuslab AB in Uppsala, Sweden. The company records contained laboratory results accompanied by a varying degree of background information on samples submitted by customers.

Sampling and analysis of CAs in air and building materials and storage and handling of data

Typically, 125–1500 l of air was sampled by pumping around 0.5 l/min through an ORBO™ 605 Amberlite® XAD®-2 100/50 mg adsorbent (Supelco, Bellefonte, PA, USA). Following desorption with 1 ml of dichloromethane (GC-quality, Sigma-Aldrich, St. Louis, MO, USA), the CAs and CPs were measured by use of standard gas chromatography–mass spectrometry (GC-MS). Briefly, 2 μl of sample solution was introduced with a multimode injector (Agilent Technologies) into a flow of helium gas (purity 6.0, AGA Gas AB). The sample molecules then passed through a 60-m Zebron ZB-5 column with 0.32 mm inner diameter

Table 1 Physico-chemical properties and odor thresholds of the 19 chloroanisole congeners (CAs)

Chemical name	CAS number	Log Kow[a]	Melting point (°C)	Boiling point (°C)	Vapor pressure at 25°C (Pa)	Solubility in water (mg/l)	Odor threshold in air ($\mu g/m^3$)[b]
2-CA	766-51-8	2.7[c]	−9.9[c]	199[c]	32[c]	490[c]	14
3-CA	2845-89-8	3.0[c]	−9.9[d]	194[c]	60[d]	235[c]	34
4-CA	623-12-1	2.8[c]	−9.9[d]	184[c]	55[d]	237[c]	2.9
2,3-diCA	1984-59-4	3.2[c]	32[c]	216[d]	17[d]	87[c]	17
2,4-diCA	533-82-2	3.2[c]	32[c]	216[d]	17[d]	87[c]	19
2,5-diCA	1984-58-3	3.4[d]	21[d]	216[d]	21[d]	76[d]	44
2,6-diCA[e]	1984-65-2	3.1[c]	21[c]	216[c]	21[d]	140[c]	0.60
3,4-diCA	36404-30-5	3.4[d]	21[d]	216[d]	21[d]	76[d]	18
3,5-diCA	33719-74-3	3.8[c]	21[d]	216[d]	15[d]	32[c]	470
2,3,4-triCA	54135-80-7	3.7[c]	70[c]	245[c]	4.5[d]	11[c]	30
2,3,5-triCA[e]	54135-81-8	3.9[c]	44[d]	245[d]	4.5[d]	17[c]	1.8
2,3,6-triCA	50375-10-5	3.6[c]	45[c]	227[c]	11[d]	30[c]	0.03
2,4,5-triCA	6130-75-2	3.9[c]	78[c]	254[c]	2.9[d]	20[c]	5.1
2,4,6-triCA[e,f]	87-40-1	4.1[c]	44[c]	245[c]	5.6[d]	10[c]	0.005
3,4,5-triCA	609-19-8	4.0[c]	101[c]	275[c]	0.36[d]	64[d]	33
2,3,4,5-tetraCA	938-86-3	4.5[c]	68[d]	273[d]	0.29[d]	1.4[c]	5.7
2,3,4,6-tetraCA[e,f]	938-22-7	4.8[c]	68[d]	273[d]	0.43[d]	2.2[d]	0.01
2,3,5,6-tetraCA[e,f]	6936-40-9	4.7[c]	89[d]	273[d]	0.28[d]	1.4[c]	3.9
PCA[e,f]	1825-21-4	5.5[c]	108[c]	298[c]	0.29[d]	0.35[d]	2.2

[a]Log octanol: water partition coefficient.
[b]Data from Strube and Buettner (2010), rounded off.
[c]Experimental data given in Epi Suite (v. 4.1) from the US EPA.
[d]Estimated using Epi Suite (v. 4.1) from the US EPA.
[e]Detected in wood samples from problem buildings.
[f]Analyzed in air samples from problem buildings (no discrimination between indicated tetraCAs).

and 1 μm film thickness (Phenomenex ApS, Værløse, Denmark), which was gradually heated from 70 to 310°C inside a gas chromatograph (Agilent Technologies, model 7890A, Santa Clara, CA, USA). This separated the molecules which sequentially eluted at the end of the column into a quadrupole mass spectrometer (Agilent Technologies, model 5975C) where they were fragmented and charged by electron ionization. The characteristic fragments of some of the 19 congeners of CAs (Table 1) and CPs were then detected in selective ion monitoring mode (SIM) using MSD ChemStation software (version E.02.02.1431, Agilent Technologies) and quantified by comparison with external reference samples (standards) containing known amounts of CAs and CPs (LGC Standards). The following substances were quantified: PCP, pentaCA (PCA); 2,3,4,6-tetraCP; 2,3,4,5-tetraCP; 2,3,5,6-tetraCA; 2,4,6-triCP; 2,4,6-triCA; and 2,4,5-triCP. Limits of quantification (LOQ) and detection (LOD) were approximately 0.5 ng and 0.25 ng, respectively (for 1 m^3 of air). The method was performed in accordance with the international standard ISO/IEC 17025:2005. The laboratory is accredited by the Swedish Board for Accreditation and Conformity Assessment with accreditation number 2085. After database extraction, it was determined that the method cannot distinguish 2,3,5,6-tetraCA from 2,3,4,6-tetraCA.

Material samples were humidified with water and then placed in a sealed glass container at 50°C (around 0.2 ml water/5 g of sample in 100 ml air volume) and sampled for 1 h. CAs emitted into air were adsorbed by solid-phase micro-extraction (SPME) onto a 85 μm polyacrylate-fused silica fiber (Supelco, article number 57304), which was then transferred to the injection port of a GC-MS where desorption took place. The analysis was performed essentially as described above for air, except that the chromatography time was longer to enhance resolution, and the characteristic fragments of CAs and CPs were detected in scan mode using MSD productivity ChemStation software (Revision E.02.00 and E.02.02) and identified using a mass spectrum library (Wiley7N, Wiley). Their amounts, expressed as fractions of total amount of substances released from the fiber into the GC-MS, are presented as qualitative data (categorical), that is, detected or not.

Data from the analyses were stored in databases using different software, and the presently used databases span over the period of May 2009 to November 2013 for material samples, and January 2009 to December 2013 for air samples. Data handling, including means and medians, was performed in Microsoft Excel.

Extraction of information from Swedish documents and toxicological evaluation of CAs

Swedish texts were identified and reviewed for information linking odor, wood preservatives, CPs, CAs, and adverse health effects. Physiochemical data on the 19 congeners of CAs (Table 1) were retrieved by use of

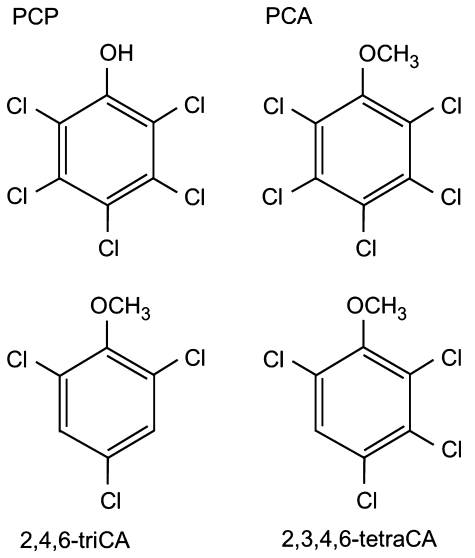

Fig. 1 Chemical structure of pentachlorophenol (PCP) and three of the 19 chloroanisole congeners (CAs) that may be formed as microorganisms dechlorinate and methylate PCP or other chlorophenols

the EPI Suite software from the US Environmental Protection Agency (see Figure 1, for examples on their chemical structure). Toxicological data were retrieved by online searches in PubMed, Google Scholar, and Web of Science. The search terms used covered the general terms pentachlorophenol and chloroanisoles as well as all individual CA congener names and their CAS numbers. Approximately 1500 publications were retrieved and were screened with respect to relevance for health effects in humans in a two-step approach, starting with the title and then the abstract. Papers deemed relevant for the toxicological evaluation were read in full.

Results

Locations and building types, levels, and congener types of CAs

Air samples. The database for air measurements contained 5833 samples of which 457 were positive for CAs and/or CPs, representing 345 buildings with 1–8 samples per building. The frequency of positive samples (8%) indicates a high frequency of affected buildings in Sweden; however, there are several possibilities for bias working in both directions. The positive samples originated from all over Sweden and with occasional ones from Norway, Finland, and Denmark. Only a few samples (1.8%) were submitted by private persons. Instead, most of the samples were provided by companies, organizations, public institutions, foundations, churches, etc. (98.2%). They were in most cases (91.7%) submitted by companies specialized on investigations of problems with building status (dampness and mold) or IAQ (health or comfort). Samples were derived from all kinds of buildings, ranging in size

Table 2 Results from air measurements in problem buildings of chloroanisoles (CAs) and chlorophenols (CPs)

Number of samples containing[a]		Measured levels (ng/m^3)[b]					
		Mean	Min	Max	Median	25 PCT[c]	75 PCT[c]
CPs	49	19.7	0.9	200	7.8	4.2	19.3
CPs and CAs	28	19.5	0.2	400	5.2	2.1	16
CAs	436	18.3	0.2	400	4.8	2.0	14
PentaCA	324	12.4	0.2	260	4.4	1.9	10
TetraCA[d]	63	36.3	1.6	400	15.0	4.6	29.8
2,4,6-triCA	164	8.7	0.2	140	2.9	1.2	10.6

[a]Results are based on 457 samples positive for CAs and/or CPs.
[b]Trace levels were not included in calculations of concentrations.
[c]PCT, percentile.
[d]2,3,4,6-tetraCA/2,3,5,6-tetraCA.

from summer cottages and detached houses to large multistory buildings (e.g., apartment houses, gymnasiums, indoor swimming pools, churches, schools, and major hospitals). Recorded total concentrations of CPs+CAs varied from trace levels to 400 ng/m^3 (Table 2). In samples with quantified CPs and/or CAs, the median total concentration was 5.2 ng/m^3. Levels of total tri-, tetra-, and penta-CAs and CPs were similar, with median values ranging from 2.9 to 15.0 ng/m^3 (Table 2). However, CAs dominated over CPs in proportion (Table 2). Thus, of the 457 positive samples, only 49 contained CPs and only 21 were positive for CPs in absence of CAs (Table 2). In contrast, 436 samples contained CAs, and 408 were positive for CAs in absence of CPs (Table 2). The types of CAs identified in the 436 positive samples were as follows: PCA 71%; tetraCAs 14% (congeners 2,3,4,6 and/or 2,3,5,6); and 2,4,6-triCA 36% (Table 2). Various combinations of CAs were found, with no obvious pattern. A majority of the 457 positive samples came from buildings with businesses or public companies and operations with altogether 116 samples taken from 77 preschools and schools. For 32 of these school buildings, the sample submitters had attached a more or less completed questionnaire from the laboratory regarding the sampled indoor environments. Odor was reported in 27 of the 32 buildings (84%) and health problems in 17 (53%) as noted by the sample submitter. The time of building construction was given for 27 schools, and in 22 cases (82%), it was reported to be between circa 1955 to circa 1980, corresponding closely to the time period in which CPs were used. Renovations with CP-treated wood may explain the occurrence of CAs in air in the five buildings outside the expected age range, except for two buildings that were relatively new.

Building material samples. Our query of the building material database for detected CPs, with or without biometabolized CAs, yielded 499 positive samples from 288 buildings, representing a wide range of indoor building materials, for example, cinders, gypsum, mineral wool insulation, asphalt-impregnated

fiberboard, plywood, and wood. Material samples had similar background as air samples (above), and only a few samples were submitted by private persons (3.2%). Of all 499 samples, 156 were derived from 77 preschools and schools (not the same as for air samples). As expected, wood was the dominant type of CP positive material, with 392 samples (222 buildings), of which CAs were identified in 250 samples (165 buildings). Wood samples containing CAs and CPs originated from various places in the buildings, for example, sills, windows, roof constructions, floors, frames in walls and around windows, outer wall paneling, glue-laminated lumber, and wood cast into concrete for attachment of walls.

Sills accounted for 105 of 134 CP positive wood samples taken from a defined location and construction type, as specified by the sample submitters. Wood samples contained CPs and CAs with different degrees of chlorination (Table 1), but all of the 250 CA positive samples contained at least one of the following: 2,4,6-triCA (42.8%); 2,3,4,6-tetraCA (86.4%); or PCA (50.4%). Unexpectedly, 178 of the total 392 wood samples positive for CPs contained neither PCP nor PCA.

Examples of problems in buildings with CAs in building materials and indoor air. A comparison of the databases for air and material samples revealed 12 buildings in which both types of samples had been submitted and found positive for CAs. Information regarding these buildings was compiled to serve as example cases (Table 3). All 12 buildings had problems with malodor as determined by an inspector and/or by residents in the buildings. Health concern and/or adverse health effects were claimed in 10 of the 12 buildings by the residents and/or by the building/environment investigators that submitted the samples. Three of these 10 buildings had received attention in local media, that is, one police station (case 1) and two preschool/schools (cases 2 and 3). In one building, a meat-producing farm (case 12), the problem was rather of economic nature as the meat was contaminated by unpleasant odor and taste resulting in complaints from customers. The buildings were generally built or renovated in the 1950 to 1970s, and material containing CPs was retrieved in various locations, but most often in the floor construction, especially in sills.

Table 3 Examples of problems in buildings with chloroanisoles (CAs) detected in building materials and indoor air

Case	Media[a]	Information on the sampled indoor environment
1	Yes	Police station. Built in the late 1950s. Treated wood in window frames. Local media reports more than 70 employees with occupational injury and mentions mold and CAs.
2	Yes	Preschool and school. Built in 1977. Treated wood in crawl space. Malodor in parts of the building. Of 50–55 people, 2–3 report sick-building symptoms (nasal congestion) disappearing when leaving the building. Some individuals in the staff have potentially developed asthma or allergy.
3	Yes	Preschool and school. Built at the end of the 19th century. Treated wood in floor beams. Odor, but not pronounced. History of sick-building symptoms among staff.
4	No	Preschool (ca. 49 pupils). Built in the early 1970s. Treated wood in sill(s). Malodor in parts of the building. One of 68 persons in the building report sick-building symptoms (nasal congestion).
5	No	School (ca. 22 pupils). Built 1970–75. Treated wood in sill(s). Strong odor. Inspection initiated by complaints from the staff.
6	No	Retirement apartments (75 residents). Built 1970s–1980s. Treated wood in sill(s). One of the residents complained about odor and health problems.
7	No	Apartment building. Built in the 1960s. Treated wood in sill(s). Malodor. Family with asthmatic children.
8	No	Detached house. Building year not determined. Treated wood in sill(s). Malodor. Family with asthma.
9	No	Detached house. Built in 1928. Renovated in the early 1960s. Treated wood in porch floor. Strange odor all over the house and two family members with sick-building symptoms. Owner identifies the malodor as 2,4,6-triCA when presented with a panel of building-related odors by the sample submitter.
10	No	Church. Built in 1808. Major renovation in 1977. Treated wood in floor beam. Malodor in parts of the building is felt most strongly when entering. Sick-building symptoms disappearing when leaving the building. One affected person working temporarily with renovation of textiles in the church.
11	No	Church. Built during the 14th and 15th centuries A.D. Treated wood in a renovated floor. Very strong odor. Inspection initiated by odor complaints from church visitors.
12	No	Farm with meat production. Built in the 1950s to 1960s. Treated wood in the roof. The owner reports problems with 'cellarlike' odor that sticks to clothes and contaminates meat.

Data were mainly retrieved from submitted questionnaires and notes made at the time when samples were submitted to the laboratory, but some information was also retrieved in retrospect by web-search and contact with sample submitters.
[a]Covered by media (such as newspapers).

Origin, scale, and characteristics of CA-related indoor problems

Swedish use of chlorophenols and authorities' position on wood preservatives. In 1941, representatives of national communication agencies formed a Wood Preservation Committee to exploit biocides for the inhibition of microbial degradation of railway sleepers and poles utilized for telephone and electricity wiring (Borup et al., 1959). With time, the committee expressed interest to expand the benefits of wood preservatives into other areas of wood consumption, including the building sector. For residential buildings, the committee expressed concern regarding the use of tar-based creosote and preservatives containing arsenic (Edén, 1954). Shortly after, in 1955, a Swedish invention called KP-Cuprinol (Richardson, 1993) based on copper and PCP was first utilized for impregnation on a small-scale (Rennerfelt, 1957). Only one year later, this product accounted for 95% of all sawn timber impregnated at private plants, as calculated by us from available raw data (Rennerfelt, 1958). From then on, consumption of KP-Cuprinol increased steadily, and the formula was included in the 1962 version of the Committee guidelines on national wood impregnation products (Träskyddskommittén, 1962). This document by the

Wood Preservation Committee was used as a reference when private and national stakeholders in the Swedish building sector published a 'Material and workmanship guide' in 1965 (ByggAMA 1965). This guide recommended the application of wood preservatives into various locations of the building envelope, as well as for renovation whenever material affected by rot needed to be substituted. Beside impregnation, other means of applying preservatives were also recommended, including dipping and brushing (painting). Adherence to the 'Material and workmanship guide' was in practice often a prerequisite for obtaining loans for building purposes (Träskyddskommittén, 1966). The 1965 guide states that preservatives that smelled badly more than one month after treatment should not be used indoors, suggesting that some odor problems had already been noted.

Still, the predecessor to the National Board of Housing, Building, and Planning (Boverket) commented in 1970 that preservatives could be used as an alternative to moisture barriers below sills in walls, and then published a Swedish Building Code (Svensk Bygg Norm 75), which stipulated the use of preservatives in crawl spaces and in locations where constructive protection of moisture could be difficult to achieve. The third revision of this Code did no longer prescribe the traditional moisture barriers below sills to prevent moisture in wood.

From the detailed annual statistics published as reports from the Swedish Wood Preservation Committee (later Institute) from 1950 to 1975, it is clear that the use of impregnated sawn wood increased more than 10-fold from 1950 to the early 1970s. After exclusion of products based on creosote and arsenic, our calculations indicate that preservation with PCP accounted for at least 79% of all impregnated sawn wood produced at private plants during this time period. Only two products containing PCP were used, that is, KP-Cuprinol and BP-Hylosan, accounting for 86% and 14% of the PCP impregnated wood, respectively.

It is unclear to us whether all impregnation occurring at private plants was recorded, as it was not made mandatory to report such operations before 1969. At that time, many small plants with rented equipment had already been active for several years (Carlbom, 2003).

Sawn wood impregnated with PCP was also exported, sometimes in ready-built houses, and mainly to Norway, Denmark, Germany, and Great Britain, but the exported amounts are difficult to estimate (Omér, 1977). Furthermore, the use of PCP for wood treatment by other methods than impregnation has not been recorded (Naturvårdsverket, 2009). However, the Swedish Chemicals Agency provides information on a wide array of products designed for dipping, remedial treatment, and for other uses in the do-it-yourself sector. Many of these products were based not only on PCP, but also on less chlorinated forms of CPs, that is, tetraCPs, triCPs, and combinations thereof. All permits for CP products were withdrawn in 1977–1978.

A few years after the ban of CPs, the Swedish Building Code was updated (Svensk Bygg Norm 80) and moisture barriers were reintroduced. The updated Code also differs from previous versions by mentioning 'nasty odor', possibly reflecting that problems had been noted in the recently erected and renovated buildings.

The Swedish record years in building (1961–1975). Starting in 1961, the building rate increased substantially and culminated between 1965 and 1974 following a government decision that resulted in the building of more than one million new homes, for a population of approximately 8 million inhabitants (Vidén, 2012). In addition, many non-residential buildings were erected in new or reformed urban districts, and many old buildings were renovated during this era of economic success in Sweden. Still in 2012, it was estimated that 30% of residents live in homes built during the 'record years', that is, 1961–1975, with two-thirds of the homes in large buildings of various sizes and one-third in small houses, mainly for single families (Vidén, 2012).

Reports of indoor environment problems associated with wood preservatives

As described in a report from the National Institute of Building Research, problems with 'nasty odor' became evident in the 1970s by an increasing number of newspaper clips describing an unpleasant odor in recently renovated buildings or relatively new buildings. Newspapers described the problems in a similar way, that is, often as a moldy odor that sticks strongly to interior textiles and clothes (Carlsson, 1974). Stigmatized residents were also described, for example, children harassed at school because they smelled badly and families who avoided social interaction. Wood preservatives were dismissed as the cause of the malodor in the affected schools, work places, and homes (Carlsson, 1974).

In contrast, wood preservatives were clearly pointed out later, in a report from the Swedish Wood Preservation Institute (Nyman, 1994) entitled *'Odor from impregnated wood'* (translated) which stated that the malodor could be *'characterized as moldy and the houses in analogy as mold houses'* (translated). Severe economic consequences for owners of problem houses were also described in that homes were costly to renovate and could be difficult to sell (Nyman, 1994). An investigation of health problems in a residential area with single family homes built in 1972–1973 is also mentioned. The residents had experienced problems with 'nasty odor' for approximately 20 years starting 1–3 years after the houses were built. Interviews with residents conducted in 15 of the 26 houses suggested allergic problems in 50% of the houses and additional non-specified health problems affecting eyes and upper

airways. Several families with extensive health problems had already left the residential area. The report points to sills impregnated with KP-Cuprinol; it states that extensive efforts had been made by many to determine the chemicals underlying the 'nasty odor' and suggests terpenes (Nyman, 1994).

Toxicological evaluation of CAs, including odor thresholds

CAs are chloromethoxybenzenes with one to five chlorine atoms on the benzene ring (Figure 1). The CAs have relatively low volatility (0.28–60 Pa at 20°C) and high boiling point (184–298°C at atmospheric pressure) (Table 1). The lipophilicity is high to very high, with octanol:water partition coefficients ranging from 500 to 300 000 (log Kow 2.7–5.5). The water solubility is low, due to the lipophilic properties. The properties of the 19 different congeners vary, in that boiling point and lipophilicity tend to increase, whereas volatility and water solubility tend to decrease with more chlorine atoms.

Odor thresholds (OTs). Young et al. determined OTs for a variety of organic compounds, including some CAs and CPs. The reported OTs were 4-CA 20 μg/l (mean) and <0.2 μg/l (lowest concentration detected), 2,4-diCA 0.5 μg/l and 0.21 μg/l, and 2,4,6-triCA 0.9 ng/l and 0.08 ng/l. The levels in the study are given as concentrations in water at 40°C (Young et al., 1996). Macku et al. refer to a study by Pereira (2007) that reports detection and recognition thresholds for 2,4,6-triCA odor in wine of 1–4 ng/l and 4–10 ng/l, respectively (Macku et al., 2009). No further details are given. However, Curtis et al. report widely different OTs: 2,3,6-triCA 0.0003 ng/l, 2,4,6-triCA 0.03 ng/l, 2,3,4,6-tetraCA 4 ng/l, and PCA 4 μg/l (Curtis et al., 1974). The thresholds are given as concentrations in water, but the temperature is not given. Staples reports an OT of 5–10 ppt for 2,4,6-triCA (Staples, 2000). No experimental details are given, and it is not clear whether the value refers to levels in air or water. Apart from reporting widely different results, a major problem with the above studies is that they were performed with CAs in aqueous solutions and that the CAs have different volatility and polarity. Therefore, the OTs in water cannot easily be translated to OTs in air. The most useful study for comparison of OTs of CAs, although carried out with five subjects only, was conducted by Strube and Buettner (Strube and Buettner, 2010) who examined the odor qualities and thresholds of all 19 congeners. The OT concentrations in air were determined with five trained subjects (four women, one man) using gas chromatography–olfactometry. The OTs ranged by five order of magnitudes, from 5 ng/m^3 for 2,4,6-triCA to nearly 0.5 mg/m^3 for 3,5-diCA (Table 1). The odor potency was clearly related to the number of chlorine atoms and, even more so, to the position of the chlorine. Thus, the ortho-substituted 2,6-diCA, 2,3,6-triCA, 2,4,6-triCA, and 2,3,4,6-tetraCA had the, by far, lowest OTs of 60, 30, 5, and 10 ng/m^3, respectively.

Toxicological evaluation. Our detailed review covering toxicokinetics, acute and subchronic toxicity, genotoxicity and cancer, and reproductive toxicity is provided as Appendix S1. Conclusions are presented in the Discussion.

Discussion

Similar to many other countries, Sweden has issued regulations to avoid excessive moisture in buildings. This also excludes the need of using toxic preservatives such as PCP to hinder microbial growth and material degradation. As demonstrated here, Swedish building regulations and practices were strikingly different in the 1960s and 1970s compared to nowadays. Furthermore, our investigation reveals several notable results.

Besides PCA, we found that many air and building material samples also contained 2,4,6-triCA and tetraCAs. This may to some extent be explained by metabolism of PCP or less chlorinated phenols contaminating the PCP used for preservation, as suggested by Gunschera et al. (2004, 2005). However, with the extensive number of material samples examined here, it becomes clear that CPs often occur in the absence of PCP. Retrieval of product information from the Swedish Chemicals Agency confirmed that many wood preservatives were based on other CP congeners than PCP. This is important to keep in mind in relation to, for example, odor perception and exposure assessment as well as health effects and toxicological evaluations.

Odor thresholds (OTs) in air of the biodegradation products of CP congeners are indeed reported to differ substantially. Thus, the OT for PCA is reported to be 2190 ng/m^3 while that of 2,4,6-triCA is 5 ng/m^3 (Strube and Buettner, 2010). Compared to data compiled for other MVOCs (Korpi et al., 2009), 2,4,6-triCA would be among the most potent microbial odors. A recent study even states that there is limited understanding of how such extremely low concentrations can still evoke an odor and provides evidence that 2,4,6-triCA distorts the perception of smell by suppressing olfactory signal transduction (Takeuchi et al., 2013). The Swedish Chemicals Agency registers four previously used preservatives based on 2,4,6-triCP and mentions the licensed companies. Two products based on tetraCPs are also registered, including KP-Cuprinol. However, for this particular preservative, there is no information regarding which company had the product permit that ended in 1977. It is remarkably difficult to find information on KP-Cuprinol, even though it is a Swedish invention that was extensively used for many years, and accounted for most of the CPs used in Swedish homes.

At the time, there was a developing concern regarding environment and health. For example, the company Bönnelyche & Thuröe (BT Kemi AB) that once distributed KP-Cuprinol was involved in a major environmental scandal suggested to have shaped the concept of environmental crime (Mårald, 2002). In the mid-1970s, approximately 700 buried oil drums containing toxic waste, including CPs, were discovered at the factory site in Teckomatorp that was associated with various complaints, including nasty odor (Svalöv Municipality, 2006). Samplings made in preparation for remediation of the site revealed various CPs both in air and soil, including 2,4,6-triCP (Sweco Viak AB, 2007). In retrospect, it could be speculated that the malodor may be at least partly due to CAs emitted from the ground as a result of biodegradation in the contaminated soil (Ide et al., 1972), as has been explored in the research field of bioremediation (Sinkkonen et al., 2013). This possibility is not unlikely as the OT for 2,4,6-triCA is extremely low.

Investigations were published also in the mid-1970s on toxic impurities in commercial PCP products. One study mentions that an unnamed product based on the sodium salt of 2,3,4,6-tetraCP was the most widely used fungicide in Sweden (Levin et al., 1976). Yet, a recent report on dioxins from the Swedish EPA describes KP-Cuprinol as being based on PCP (Naturvårdsverket, 2009). However, the report mentions that the chlorophenolate was supplied by the Finnish company Kymmene AB. Their trade name formulation Ky-5 is described in a Finnish doctoral thesis as consisting mainly of 2,3,4,6-tetraCP (70–80%) with the remaining part being 2,4,6-triCP and PCP (Lyytikäinen, 2004). According to the thesis, Finland imported a similar formulation from the USA for approximately ten years before the production of Ky-5 started in the 1940s. This suggests that products referred to as PCP may primarily be based on other types of CPs also in other countries than Sweden. Even commercial brands, when based on PCP, generally contained 4–12% of 2,3,4,6-tetraCP (WHO, 1987).

Many types of CAs and other anisoles may be formed from the various impurities that occur in technical PCP (Crosby, 1981). In the IAQ setting, it is of considerable relevance that 2,3,4,6-tetraCP was a major constituent in many wood preservatives as the corresponding biomethylated 2,3,4,6-tetraCA is reported to have an extremely low OT of 10 ng/m^3. This is close to the 5 ng/m^3 reported for 2,4,6-triCA in a comparative study (Strube and Buettner, 2010). Importantly, these OTs are in the range of the recorded indoor concentrations in our study. In addition, some people will be able to sense the smell of CAs even below the reported OTs due to method constrains and interindividual variability in olfactory functioning in populations (Walker et al., 2003).

Given the extremely low OTs of 2,4,6-triCA and 2,3,4,6-tetraCA, it is not surprising that even limited microbial activity and areas of moisture exposure are sufficient to cause problems with IAQ. Thus, it has been reported that moisture-damaged preserved wood smell considerably despite very little mold growth (Nyman, 1994), that moisture-damaged preserved wood smell more than moisture-damaged unpreserved wood (Björk and Mattson, 2002; Nyman, 1994), and that crawl spaces with visible preserved wood smell more often than crawl spaces with unpreserved wood (Boverket, 2010).

We demonstrate the common occurrence in Sweden of both 2,4,6-triCA and 2,3,4,6-tetraCA in treated wood and indoor air. While these CAs have received minimal attention in the field of IAQ, they are well known to cause problems in other areas. Both molecules are fouling contaminants of water (Nystrom et al., 1992) caused, for example, by pulp mill effluents of CPs used for the control of slime (Paasivirta et al., 1992), as well as of a range of food items (Curtis et al., 1972; Engel et al., 1966; Whitfield et al., 1985) and beverages (Miki et al., 2005; Spadone et al., 1990), including wine where they cause the so-called cork defect (Buser et al., 1982). Both CAs were also identified in relation to contamination of goods during packaging and transportation (Whitfield et al., 1985), for example, in containers with wood flooring treated with CPs (Hill et al., 1995). The source of contamination is not always clear. This is exemplified by an incident where musty odor in solid oral pharmaceutical products was attributed to contamination of minute amounts of 2,4,6-triCA and 2,3,4,6-tetraCA permeating the high-density polyethylene product bottles during shipping (Ramstad and Walker, 1992). Altogether, CAs have major implications for the food and wine industry, where contamination is often described as earthy, muddy, musty, moldy, or fungal (AFGC, 2007; Coque et al., 2006).

The ability to stick to, and penetrate through, materials is typical of CAs also in the built environment, and we present evidence that 'contaminating' mold odor was reported in Swedish media as early as already in the beginning of the 1970s and that it occurs still today.

As demonstrated here, Swedish building regulations in the 1960s and 1970s promoted chemical treatments of wood while abandoning traditional constructive methods to avoid moisture. It seems likely that many, perhaps most, of the buildings erected or renovated during this time had preservatives in one or several parts of the construction. It is also plausible that CPs often were the chosen biocide as concern was raised at the time regarding alternative treatments with creosote and arsenic. Unfortunately, these building practices coincided with the Swedish record years in rate of building and renovation between 1961 and 1975. As CPs were used both before and after the record years, it can be argued that many inhabitants spent and still spend considerable time in buildings containing CPs,

at home, at school, at work, etc. Arguably, this led and still leads to significant exposure to CAs biogenerated from CPs in the damp locations that the preservatives were aimed for. Future exposure may even increase as the climate becomes warmer and more humid.

Upon uptake by inhalation, CAs may be demethylated into the corresponding CPs, but exposure studies rarely consider other congeners than PCP. This inadvertence means that the overall exposure to CPs may have been severely underestimated. Still, one study designed to determine PCP and other types of halogenated environmental contaminants in blood plasma in Swedish and Latvian men did find that PCP levels were much higher in Swedes than in Latvians. The authors conclude that there must be unidentified sources of PCP in the environment, and they speculate that exposure to PCP, due to its use as a wood preservative, occurs via indoor air (Sjodin et al., 2000). We believe that this was a correct assumption and refer, as do the authors, to a report that covers indoor exposure to PCP in general terms (WHO, 1987).

Although no Swedish studies have taken CAs into account, national reports on residence and health by public authorities show an overrepresentation of unspecific building-related illness in buildings from 1961 to 1975 (Socialstyrelsen, 2009), of asthma/allergic rhinitis in children (IMM, 2013), and of mold odor reported by building inspectors (Boverket, 2010). The latter report states that one-third of all crawl spaces with visible preserved wood had a nasty odor that was perceived by building inspectors as mold odor. As there is public awareness of adverse health effects, it seems likely that residents become concerned and stressed by living or spending time in moldy and/or moisture-damaged buildings. In Sweden, indoor malodors are often taken seriously, and legislation states that microbial growth and odor is not acceptable in, for example, apartment buildings, public buildings, and non-industrial workplaces and also stipulates that acts should be taken by landlords and business operators to secure a healthy environment. Sometimes, laboratory analyses are utilized in this context, and when CAs are detected, it is common that exposed residents become alarmed and ask questions on health effects. Their concern is often strengthened by the fact that national authorities provide little if any information on CAs and the historical context, which therefore is highly warranted.

When addressing the potential risk of CAs in indoor air, it is crucial to determine the types and levels that occur. Our data are limited in that not all 19 CA congeners were measured. Still, the particular analytical methodology used (other adsorbents and ways of desorption exist) enabled detection in air of the CAs that dominated in wood samples (PCA, 2,3,4,6-tetraCA, 2,4,6-triCA), and that could be expected to dominate in air based on the CPs used in Swedish wood preservatives. This is true also for the data on CPs in air, although their levels may have been underestimated for technical reasons (they may be better captured by other sampling and analytical methods).

Our toxicological evaluation is limited, such that few toxicological data are available, only PCA was studied, via the oral route only, and no data were found on reproductive toxicity. Nevertheless, it does provide sufficient information to inform concerned stakeholders. In short, PCA has an intermediate toxicity with LD_{50}-values around 300 mg/kg bodyweight in rodents. Further, there is some evidence of a weak genotoxic potential and of carcinogenicity in rodents at daily doses of 40 mg/kg/day. The carcinogenicity is likely mainly indirect due to metabolic overload and cytotoxicity; thus, a threshold for cancer is to be expected. For comparison, a 70-kg person residing in a problem building with 10 ng/m^3 PCA in the air would inhale (20 m^3/day $\times$ 10 ng/m^3/70 kg) = 3 ng/kg/day, that is, seven orders of magnitude lower than the doses used in the rodent studies. Except for the possibility of odor-related adverse effects, there is no indication that inhalation exposure would cause substantially different toxic effects compared to oral exposure.

We conclude that PCA is highly unlikely to cause 'classical' toxicity or cancer at the exposure levels generally seen in problem buildings. In view of the minute exposure levels, toxic and carcinogenic effects are unlikely also for the other CAs, although no data were found in the literature.

However, we do suggest that malodor (such as that from CAs) should be considered as an adverse effect on health and well-being. The European Scientific Committee on Occupational Exposure Limits (SCOEL), for example, takes a similar position. Thus, SCOEL considers that not only symptoms, such as ocular or nasopharyngeal discomfort or irritation, but also nuisance due to smell might be regarded as an adverse effect and thereby serve as basis for setting a health-based OEL (SCOEL, 2013). Still, development of criteria for nuisance from malodor remains difficult due to the essentially subjective nature and wide interindividual variability of such perceptions.

Although our toxicological evaluation suggests that no health risk is expected *per se*, CAs may still contribute to symptoms and health effects that associate with dampness in buildings, for example, unspecific building-related illness, asthma and allergy, and with olfaction playing a major role (Claeson et al., 2009; Shusterman, 2002). Unpleasant odors have previously been assumed to contribute to development of health symptoms in sensitive individuals (Shusterman, 2002), and potential influencing factors have been identified (Shusterman, 2001), for example, worries about annoying odors (Shusterman et al., 1991), beliefs, and expectations about their potential risk (Claeson et al., 2013; Nordin et al., 2013), existing pre-knowledge about the perceived odor, and other individual charac-

teristics (Dalton, 1999, 2002). The main task of the olfactory sense is to direct attention to the odorous source and, by integration with prior experience, for example, beliefs of the chemical exposure, guide the individual to avoid, or approach the source (Engen, 1991; Stevenson, 2010). When the individual believes the source to be hazardous, the odor will be perceived as unpleasant, negative emotions will be evoked, and a stress response will be induced by the autonomic nervous system (ANS). The unpleasantness of the odor and the stress response will increase the likelihood of behavioral avoidance of the source (Djordjevic et al., 2008; Nordin et al., 2013). This impact of beliefs of the exposure is a type of top-down processing (Neisser, 1967) and is a characteristic feature of olfaction (Dalton, 2012; Stevenson, 2010). Common stress-related ANS responses include symptoms such as headache, fatigue, concentration difficulty, palpitation, and nausea, which commonly are associated with poor IAQ. As CAs have a moldy odor and as the general belief is that mold even at low doses is toxic (Chang and Gershwin, 2005), olfaction may well be a mediating factor between CA exposure and health problems.

In addition to evoking odor perception, odorous molecules may also activate the chemesthetic sensory system that evokes sensations of irritation in the nasal cavity, cornea, and throat. This sensory system also has the potential to trigger protective physiological reflexes, to make the individual alert for danger, and to start flight behavior (Cain, 1988). These physiological reflexes are intended to repel chemicals attached to body tissue and include symptoms such as coughing, tearing, and sneezing. These symptoms, together with irritation in the nasal cavity, cornea, and throat, are all very common symptoms in poor IAQ, suggesting that chemesthesis may also be a mediating factor between building emission exposure and health problems.

Although irritation is unlikely to occur for CAs at the minute levels measured in this study, it may be difficult to discriminate between the effects of chemesthesis and olfaction (Wolkoff et al., 2006). Furthermore, the stress response evoked by both annoying odor and sensory irritation may release neuropeptides, such as corticotropin-releasing factor and substance P. These neuropeptides mediate inflammation and are thereby likely to worsen many of the symptoms associated with poor IAQ, but do also mediate stress, and may thus aggravate the stress-related symptoms (Black, 2002).

Altogether, the described psychobiological mechanisms could be triggered by any of the more than 200 described MVOCs (Korpi et al., 2009) that may be perceived as mold, for example, geosmin, 2-methylisoborneol, 1-octen-3-ol, and dimethyl disulfide, or by any other annoying volatiles that can be perceived by olfaction at the minute levels typically reported in homes and offices with IAQ problems (Korpi et al., 2009; Wolkoff et al., 2006).

Thus, malodor is of obvious relevance in the areas of IAQ research that deal with human perception of air as being acceptable and fresh, and having a positive impact on performance and productivity (Fanger, 2006). In addition, we suggest that annoying odor may also contribute to adverse health effects and recognize that information to those exposed may affect both comfort and health.

In conclusion, we add to previous studies on CAs (Gunschera et al., 2004, 2005) by providing extensive data on CA and CP congener types and levels occurring in building materials and indoor air, by performing a toxicological evaluation, and by covering the psychobiological aspects of chemosensory perception. As CAs apparently remind people of mold, do not normally occur indoors, and are relatively easy to measure, they should be most relevant targets for further studies.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:
Appendix S1. Toxicological evaluation

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