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Risk assessment concepts and approaches for indoor air chemicals in Japan

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ABSTRACT

Individuals living in general indoor environments are exposed to a greater variety of chemical pollutants, albeit at lower concentrations, compared with industrial workers in occupational environments. These pollutants can result in a variety of adverse health effects, including those affecting the respiratory, neurological, reproductive, dermatologic, and cardiovascular systems. In Japan, indoor air quality guidelines have been established for 13 chemicals since 1997, and these developments have continued on the basis of scientific discussions in the Committee on Indoor Air Pollution (CIAP) that was set up by the Ministry of Health, Labour and Welfare. However, the types and concentrations of these pollutants have been observed to be inconsistent over time due to lifestyle changes and the development of novel household products and building materials. Therefore, continuing the monitoring of indoor chemicals and the development of indoor air quality guidelines for substances that pose potential high health risks are essential for the protection of public health. In indoor environments, there are multiple media by which humans come in contact with indoor chemicals and multiple exposure pathways that can affect human health, particularly for semi-volatile organic compounds (SVOCs). This is defined as aggregate exposure. Furthermore, combined exposure to multiple low-level pollutants occurs in indoor environments. In this article, a comprehensive overview of the indoor air quality guidelines in Japan and assessment approaches for developing indoor air quality guidelines is provided. In addition, future issues facing approaches for indoor chemicals, including aggregate exposure to SVOCs and combined exposure to multiple pollutants with common toxicological effects in indoor environments, are discussed.

1. Introduction

Indoor air quality (IAQ) is an important determinant of human health. People in modern societies spend more than 90% of their time indoors, i.e., in their homes, workplaces, schools, transportation, and public spaces (Brasche and Bischof, 2005; Leech et al., 2002). Individuals living in indoor environments are typically exposed to a greater variety of chemical pollutants, albeit at lower concentrations, compared with industrial workers in occupational environments. These pollutants can have a variety of adverse health effects, including those affecting the respiratory, neurological, reproductive, dermatologic, and cardiovascular systems (Wu et al., 2007). Hence, a high level of protection against adverse health effects resulting from inadequate IAQ should be assured.

In the 1990s, public health problems caused by chemical indoor air pollutants were a cause of considerable public concern in Japan. After conducting extensive exposure assessments, the Ministry of Health, Labour and Welfare (MHLW) established IAQ guidelines for 13 chemicals, including formaldehyde, toluene, and xylene from 1997 to 2002, based on scientific discussions in the Committee on Indoor Air Pollution (CIAP) (Azuma et al., 2007, 2008; MHLW, 2000a, 2000b; MHLW, 2001; MHLW, 2002). In addition, the National Building Codes and formaldehyde emission standards used to monitor building materials were revised (Azuma et al., 2008). However, neither the types nor the concentrations of chemicals found indoors are consistent. Changes occur day-to-day, month-to-month, year-to-year, and decade-to-decade with changes in lifestyle, the development of novel household products and building materials, and the development of new measurement technologies (Weschler, 2009). Adverse health effects caused by semi-volatile organic compounds (SVOCs) have been reported over the past

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decade (Bornehag and Nanberg, 2010; Jaakkola and Knight, 2008; Lyche et al., 2009). Therefore, the MHLW started to establish new (or update) IAQ guidelines from 2012, and the CIAP was relaunched. Extensive exposure assessments for housing were performed in Japan, and the CIAP proposed a new approach to develop IAQ guidelines based on these health risk assessments.

This article aims to provide a comprehensive overview of the Japanese approaches to regulate the levels of indoor air chemicals. In particular, we highlight the risk assessment concepts used to reduce adverse health effects of indoor air chemicals. In addition, future issues regarding multi-route and multi-media exposure to SVOCs as well as multiple exposures to indoor air chemicals and their combined health effects are discussed.

2. Approaches to ensuring adequate IAQ

2.1. Basic concepts used to regulate indoor air chemicals

There are several important barriers to developing policies to improve the air quality in indoor environments. One major difficulty in regulating indoor air is that it is not the responsibility of a single department or ministry and, in many countries, no specific laws comprehensively addressing the subject exist. Regulation can also affect the privacy of individuals (Seifert, 1992). In addition, a single measurement of indoor chemical pollutants does not represent the air quality in a particular indoor environment because indoor chemical pollutant concentrations change in accordance with indoor temperature and time-dependent reductions in source emissions. The concentration of an indoor chemical pollutant depends on the relationships between the volume of air contained in the indoor space, the rate of production or release of the pollutant, the rate of removal of the pollutant from the air via reaction or settling, the rate of air exchange with the outside atmosphere, and the outdoor pollutant concentration (Jones, 1999). Furthermore, indoor air chemicals emanate from a range of sources. They are emitted by the fabric of buildings and can also be a by-product of the activities that are undertaken within them.

Sources can be broadly classified as being associated with the activities of building occupants and other biological sources, the combustion of substances for heating or fuel, and emissions from building materials. For some contaminants, infiltration from outside, either through water, air, or soil, can also be a significant source (Jones, 1999; Wu et al., 2007). Therefore, the indoor environment does not lend itself to the regulatory approach typically used to limit ambient air pollutants, i.e., the setting of standards. Thus, guideline values, rather than standards, are used to regulate IAQ (Harrison, 2002; Levin, 1998; Seifert, 1992; Seifert et al., 1999).

Guideline values for specific indoor air chemicals have been developed by the World Health Organization (WHO) Regional Office for Europe (WHO Europe, 2010) and agencies or ministries of health or environment in several countries such as Germany (Fromme et al., 2019), Canada (GC, 2018), France (ANSES, 2018), and Japan. This strategy both protects the public from health effects due to indoor chemical pollutants and promotes the prevention of pollution. Furthermore, such guideline values, together with appropriate modeling, can serve to limit emissions, especially those from building materials and household products (Seifert, 1992).

2.2. IAQ guidelines in Japan

2.2.1. Concepts of IAQ guidelines

In order to protect public health, unnecessary exposure to indoor chemicals should be minimized and chemicals should be safely and appropriately used so that they have no adverse effects on human health (MHLW, 2019). The guideline values for indoor air concentrations are set so that, according to currently available scientific knowledge, no adverse health effects would be expected to occur in humans, even if exposures to the chemicals at the levels decided continue throughout life. IAQ guidelines are applied to all indoor spaces, including housing, offices, medical facilities, welfare facilities, schools, [illegible]c facilities, and transportation facilities, but exclude specific [illegible]s such as industrial plants. These values may be revised in the future as necessary depending on further available knowledge and/or progress in international assessment based on such scientific knowledge (MHLW, 2000a, 2000b; MHLW, 2001; MHLW, 2002; MHLW, 2019).

2.2.2. Toxicologically based guideline values for 13 chemicals

In 2000, as a means to set the priority of indoor air chemicals for which guideline values should be established, the CIAP considered the following six criteria (MHLW, 2000a):

(1) Guideline values for indoor air chemicals that have already been set by other governmental agencies or international organizations; for example, the WHO Air Quality Guidelines.
(2) Air pollutants for which indoor concentrations are higher than those outdoors because of indoor emission sources in residential environments.
(3) Public complaints about indoor air chemicals such as total volatile organic compounds (TVOC).
(4) New regulations for indoor air chemicals already established by other foreign governments; for example, chlorpyrifos or diazinon by the United States Environmental Protection Agency.
(5) Rules covering major uses of chemicals in construction, such as solvents, adhesives, insecticides, plasticizers, and termiticides.
(6) Rules covering major chemical structural categories of volatile organic compounds (VOCs), including aldehydes, ketones, aromatic hydrocarbons, halocarbons, alkanes, terpenes, esters, and alcohols.

According to the fourth criterion, new regulations focus on building products or consumer products used inside the buildings. The fifth and sixth criteria are applied to indoor chemicals having similar uses or chemical structures with substances mentioned by the established IAQ guidelines. As a result, IAQ guidelines for 13 chemicals were established (Table 1) on the basis of scientific discussions in the CIAP.

The guidelines regarding acceptable values for indoor air concentrations of these chemicals were established on the basis of the studies measuring chronic toxicity over long-term exposure. However, one exception is formaldehyde, which was given a 30-min average value based on toxicity over short-term exposure. This is because the main objective of formaldehyde exposure is to avoid short-term irritation and consecutively repeated irritation. Toxicologically based guideline values are derived from the toxic effects and dose-response relationships for critical toxic endpoints based on the recommendations of the WHO (WHO, 1999).

For substances with a threshold in the dose-response relationship, critical effect levels as a point of departure (POD), such as lowest-observed adverse effect level (LOAEL) or no-observed adverse effect level (NOAEL), are determined. Then, various assessment and extrapolation factors are applied to the POD, as shown in Table 1. For substances with no threshold in the dose-response relationship, such as genotoxic carcinogens, unit risk is calculated. In general, an air concentration corresponding to a lifetime excess cancer risk of 1/100,000 (10^{-5}) is used as the guideline in Japan (Kawamoto et al., 2011).

In these processes, when critical effect levels of inhalation exposure are not identified, critical effect levels derived from oral exposure studies are used. This is based on the assumption that chemicals that cause adverse health effects after exposure by ingestion cause health effects at the same target site after intake into the body by inhalation (and *vice versa*) (OEHHA, 2005). This assumption depends on the critical effects of the chemical. This assumption is acceptable for the systemic effect but not for the local effect, such as respiratory versus digestive. To make this conversion, a reference human body weight of 50 kg and a reference human respiration rate/day of 15 m^3 are used.

Table 1
Guidelines for indoor air quality.

Substances	Point of departure[a]	Critical toxic endpoint	Assessment and extrapolation factor[b]	Guideline value (μg/m^3)	Date of establishment	Reference
Formaldehyde	Inhalation 0.1	Nose and throat irritation in humans	Not applied	100	1997.6.13	WHO Europe (1996)
Toluene	Inhalation LOAEL 332	CNS and reproductive effects in humans	ACE: 4.2, UF1: 10, UF4: 10, Potential effects on the developing CNS: 3	260	2000.6.26	Foo et al., (1990), 1993, Ng et al., (1992)
Xylene	Inhalation LOAEL 61	CNS effects in humans	UF1: 10, UF4: 10, Lack of chronic neurological effects: 3	200 (870 previous value)	2019.1.17 revision (2000.6.26 initial)	Uchida et al. (1993)
1,4-Dichlorobenzene	Oral NOAEL 10	Liver and kidney effects in dogs	ACE: 1.4, UF3: 10, UF4: 10, AIE: 0.3	240	2000.6.26	Naylor and Stout (1996)
Ethylbenzene	Inhalation NOEL 2150	Liver and kidney effects in mice and rats	ACE: 5.6, UF 3: 10, UF4: 10	3800	2000.12.15	NTP (1992)
Styrene	Inhalation LOAEL 1260	Brain and kidney effects in rats	ACE: 5.6, UF1: 10, UF 3: 10, UF4: 10	220	2000.12.15	Savolainen and Pfäffli (1977), Vainio et al., (1979)
Chlorpyrifos	Oral LOAEL 0.3	Neurological effects in maternal rats and morphological effects of brain in the neonatal infants	UF1: 10, UF 3: 10, UF4: 10, AIE: 0.3, Additional UF for brain effects in children: 10	1 for adults, 0.1 for children	2000.12.15	Hoberman (1998), USEPA 2000a,b
Di(n-butyl) phthalate	Oral LOAEL 2.5	Reproductive and developmental effects in rats	UF1:5, UF3:10, UF4: 10, AIE: 0.3	17 (220 previous value)	2019.1.17 revision (2000.12.15 initial)	Lee et al. (2004)
Tetradecan	Oral NOAEL 100	Liver effects in rats	UF2: 10, UF3: 10, UF4: 10, AIE: 0.3	330	2001.7.5	TPHCW (1997)
Di(2-ethylhexyl) phthalate	Oral NOAEL 3	Reproductive and developmental effects in rats	UF3:10, UF4: 10, AIE: 0.3	100 (120 previous value)	2019.1.17 revision (2001.7.5 initial)	Christiansen et al. (2010)
Diazinon	Oral LOAEL 0.026	Neurological effects in rats	UF1: 3, UF3: 10, UF4: 10, AIE: 0.3	0.29	2001.7.5	USEPA (2000c)
Acetaldehyde	Inhalation NOEL 270	Effects on olfactory epithelium in rats	ACE: 5.6, UF2 combined with possible cancer effect: 10, UF3: 10, UF4: 10	48	2002.1.22	Appelman et al. (1986)
Fenobucarb	Oral NOEL 4.1	Neurological effects in rats	UF3: 10, UF4: 10, Difference of absorption rate in inhalation exposure: 4 AIE: 0.3	33	2002.1.22	Mitsubishi Chemical Corporation (1990)
TVOC	As low as reasonably achievable from nationwide survey of VOCs			400 tentative target value	2000.12.15	MHW (1999)

[a] Inhalation (mg/m^3). Oral (mg/kg/day).

[b] UF1, LOAEL to NOAEL extrapolation; UF2, Extrapolation across durations; UF3, Interspecies extrapolation; UF4, Intraspecies extrapolation. Abbreviations: ACE, adjusting from discontinuous exposure to continuous exposure (24 h per day, 7 days per week); AIE, adjusting from oral intake to inhalation exposure (human body weight of 50 kg and human respiration rate/day of 15 m^3); CNS, central nervous system; LOAEL, lowest-observed adverse effect level; NOEL, no-observed effect level; NOAEL, no-observed adverse effect level; UF, uncertainty factor; TVOC, total volatile organic compounds; VOCs, volatile organic compounds.

2.2.3. Non-toxicologically based advisable value for TVOC

The individual guideline values for indoor air chemicals is based on toxicological data. However, a large number of indoor air chemicals have been detected (MHW, 1999; MHLW, 2000a), and establishing individual guideline values would require a great amount of time. Furthermore, the health risks from potentially hazardous chemicals whose guideline values are not yet established may increase in the future. Hence, the CIAP adopted the TVOC approach as an important indicator to limit the indoor air pollution (MHLW, 2000b). The TVOC value indicates the total amount of individual VOCs as derived from a gas chromatography/mass spectrometry (GC/MS) curve from n-hexane to n-hexadecane (JRC, 1997).

Originally, the CIAP did not have sufficient reliable scientific knowledge to establish the guideline value of TVOC based on the available toxicological data. Consequently, the CIAP recommended a tentative target value of 400 μg/m^3 from the median value calculated using the results of a nationwide field survey on VOCs (MHW, 1999), based on the concept of "as low as reasonably achievable" (ALARA) (MHLW, 2000b). The association between TVOC concentration and indoor health effects or complaints, like building-related symptoms, sensory irritations, or chemical intolerance, is not straightforward (Wolkoff and Nielsen, 2001). Hence, the TVOC target value should be used as an indicator for IAQ, independently of individual VOC guideline values.

2.3. Effect of setting IAQ guidelines

Since IAQ guidelines were established from 1997 to 2002, the mean indoor air concentrations of formaldehyde, toluene, xylene, and ethylbenzene in the nationwide survey on housing notably decreased from [illegible] to 2005; i.e., from 89.6 to 29.5 μg/m^3 for formaldehyde, 154.2 to 11.3 μg/m^3 for toluene, 26.0 to 4.3 μg/m^3 for xylene, and 43.4 to 4.3 μg/m^3 for ethylbenzene. However, this tendency was not observed for acetaldehyde from 2002 to 2005 (30.6–30.6 μg/m^3) (Osawa and Hayashi, 2009).

The main emission source of formaldehyde is adhesives for wood-based materials, and shipments of formaldehyde-based adhesives decreased since setting the guideline. The main emission sources of toluene, xylene, and ethylbenzene are solvent-based paints, and shipments of such paints have also decreased (Azuma et al., 2008). The efforts of the related industries resulted in those reductions. However, there are numerous sources of acetaldehyde emissions in indoor environments, such as construction lumber, incomplete combustion in appliances, environmental tobacco smoke, drinking alcohol, and fragranced consumer products (Yamashita et al., 2010). Generation from these sources largely depends on occupant lifestyle, and secondary acetaldehyde sources can make it difficult to reduce indoor air concentration. 1,4-Dichlorobenzene is used for indoor household insect repellents, the usage of which in buildings depends on the lifestyle of the occupants. The health risk of 1,4-dichlorobenzene remained at a high level in the results of a nationwide survey of housing conducted from 2012 to 2014 (Azuma et al., 2016). Thus, additional approaches for the risk management of substances that depend on the lifestyles of building occupants are required.

2.4. New scheme for developing IAQ guidelines

The CIAP proposed a new scheme for developing IAQ guidelines based on health risk assessments, including the priority of the indoor air chemicals for which guideline values should be established (Fig. 1) (MHLW, 2013a). According to the new scheme, preliminary exposure assessments are initiated on the basis of the exposure data compiled from nationwide field surveys, emissions from household products, or epidemiological studies. Subsequently, preliminary risk assessment is conducted using data from the exposure assessments and existing hazard data. Then, priority-setting for developing IAQ guidelines is carried out based on the risk levels. To obtain the POD for hazard assessment, the latest documents and reports published by international and national agencies are reviewed, and toxicological or epidemiological studies are searched using databases of medical and scientific literature. The most sensitive toxic endpoint is selected to minimize the risks associated with chemical exposure.

The National Institute of Health Sciences, which is a major organization within the MHLW, conducted nationwide field surveys on the indoor air concentrations of chemicals in housing from 2011 to 2013 (MHLW, 2013b, 2013c, 2014). Based on these surveys, the CIAP conducted preliminary exposure and risk assessments for chemicals detected in the nationwide field survey (MHLW, 2016). Table 2 shows a summary of the preliminary exposure and health risk assessments that are combined with the results of those nationwide field surveys.

In order to help risk assessors assist risk managers in making judgments on the overall level of concern and in prioritization of competing hazards, several bodies have proposed the use of margin of exposure (MOE) for comparative risk assessment (Omenn et al., 1997; WHO, 1999; WHO, 2006). MOE reflects the ratio between a level associated with toxic effects and the actual level of exposure in a particular situation (Omenn et al., 1997). The CIAP adopted the MOE approach for characterizing health risks from exposure to indoor air chemicals measured in the nationwide field surveys. The results show that the risk levels for 2-ethyl-1-hexanol, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate (TMPD-DIB), and 2,2,4-trimethyl-1,3-pentanediol monoisobutyrate (TMPD-MIB) indicate a "potential for health risk" because of their low MOEs. In the detailed risk assessment, the major uses and emission sources of chemicals that the IAQ guidelines were previously established as well as further detailed data on exposure, are considered for the management of novel target chemicals for developing IAQ guidelines. Furthermore, currently available methods of measurement and the confirmation of appropriate political effects are also considered. The IAQ guidelines for these three chemicals are under development by the CIAP.

3. Future issues for approaches to indoor chemicals

Mechanisms for single route of exposure via inhalation and exposure to a single chemical are generally considered in the existing IAQ guidelines. However, there are multi-route and multi-media mechanisms of exposure for specific indoor chemicals. Exposure to a single chemical through multiple routes and from multiple sources is defined as an aggregate exposure (Kienzler et al., 2016; Meek et al., 2011). In addition, when there are multiple exposures to indoor chemicals, combined health effects are often a cause for concern. An instance of exposure to multiple chemicals is defined as a combined exposure. The aggregate and combined exposures from mixtures occur upon exposure to various chemicals including VOCs, SVOCs, and particulates. In this section, we discuss these two future issues regarding risk assessment approaches for indoor chemical exposure. In particular, we focused on indoor exposure to SVOCs as examples of aggregate exposures.

3.1. Multi-route and multi-media exposure (i.e., aggregate exposure) to SVOCs

SVOCs include a vast array of plasticizers, flame retardants, pesticides, biocides, preservatives, sealants, surfactants, waxes, and polishes. They are widely used as additives in many building materials, furniture products, carpets, and consumer products (Lucattini et al., 2018; Weschler and Nazaroff, 2008). Vapor pressures of these SVOCs between 10^{-14} and 10^{-4} atm (10^{-9} to 10 Pa) have been proposed. Many phthalates, perfluorinated compounds, organophosphate compounds, chlorinated compounds, brominated compounds, and siloxanes are classified as SVOCs. Furthermore, SVOCs are found in both the gas and condensed phases and redistribute from their original sources over time to indoor air, indoor dust, and other indoor surfaces (Weschler and

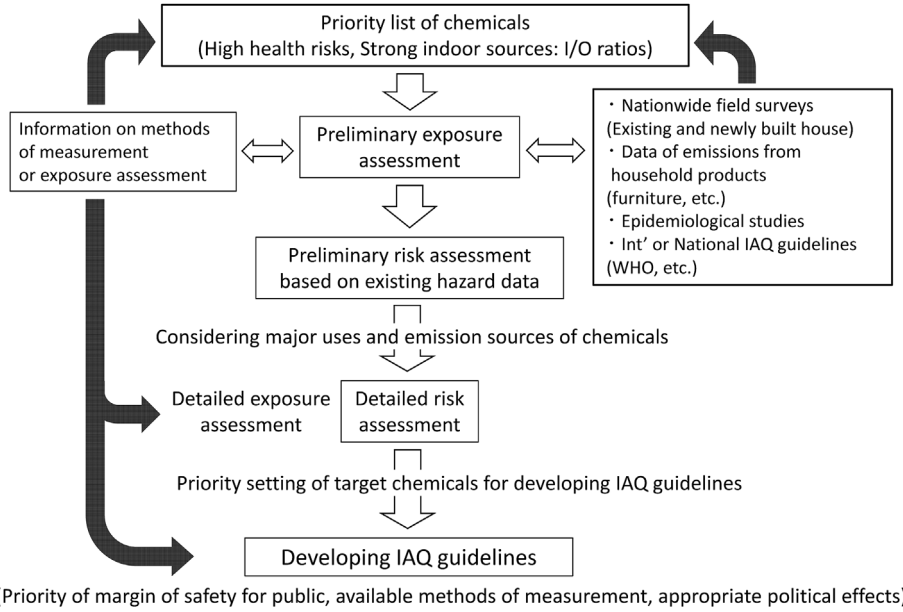

Fig. 1. Scheme for developing indoor air quality guidelines. Abbreviations: IAQ, indoor air quality; I/O, indoor/outdoor; Int', international; WHO, world health organization.

Nazaroff, 2008).

Phthalates are ubiquitous chemicals found in many consumer products and plasticizers. They impart flexibility and durability to resins such as polyvinyl chloride (Huber et al., 1996). Phthalates can be released into the environment through leaching, evaporation, migration, and abrasion. Due to their widespread use, the general population is constantly exposed to phthalates in everyday life through ingestion, inhalation, and skin absorption from indoor air, indoor suspended particles, indoor dust, and contaminated food or drinking water (Bekö et al., 2013; Hauser and Calafat, 2005; Koch et al., 2013; Weschler and Nazaroff, 2008; Wormuth et al., 2006). This multi-route and multimedia exposure is defined as aggregate exposure (Kienzler et al., 2016). These situations and relationships are illustrated in Fig. 2.

In study on Danish children, Bekö et al. (2013) reported that exposures to air and dust in the indoor environment for diethyl phthalate (DEP), di(n-butyl) phthalate (DnBP), and di(isobutyl) phthalate (DiBP), which have higher vapor pressures, accounted for approximately 100%, 15%, and 50% of the total intake, respectively, with dermal absorption from the gas-phase being the major exposure pathway. More than 90% of the total intake of butyl benzyl phthalate (BBzP) and di(2-ethylhexyl) phthalate (DEHP), which have lower vapor pressures, came from sources other than indoor air and dust. Guo and Kannan (2011) reported that dietary intake and dermal absorption were important but mutually-interfering sources of DEP exposure in the USA, whereas dietary intake was the main source of BBzP exposure (> 58%) and DEHP exposure (> 86%). Inhalation, dermal absorption, and dietary intake were mutually-interfering main sources of DiBP.

To reduce the health risks due to chemical pollutants via such these multi-route exposures, risk management based on estimates of the total body burden of the pollutants and the relative contributions (i.e., allocation) of these exposures to the total body burden should be performed. Therefore, some consideration of the proportion of the acceptable daily intake (ADI) or tolerable daily intake (TDI) attributed to different exposure sources is needed for developing guideline values and risk management strategies. This approach ensures that total daily intake from all exposure sources does not exceed the ADI or TDI.

In Japan, this approach was used in the development of ambient environmental quality standard for dioxins. Over 90% of human daily intake of dioxins results from the consumption of food containing dioxins. The major environmental sources of dioxins are emissions from combustion, waste incineration, and production process of industrial chemicals. Aerial transport of these emissions is the primary pathway by which dioxins enter the terrestrial environment and food chain (WHO, 2000). Therefore, setting a standard for dioxins in ambient air was required. Before developing an ambient environmental quality standard for dioxins, the Environment Agency (EA, currently the Ministry of the Environment) and the Ministry of Health and Welfare (MHW, currently the MHLW) set a TDI of 4 pg-TEQ/kg/day for dioxins based on toxicological data from animals (EA and MHW, 1999). Then, in 1999, the EA established an annual average ambient environmental quality standard of 0.6 pg-TEQ/m^3 for dioxins based on the TDI along with the assumptions that i) the internal absorption rate of dioxins is 50% from food and 85% from ambient air; and ii) the allocation rate of ambient air is 5–15% of the total intake of dioxins in general populations (Kawamoto et al., 2011).

This allocation approach has also been reported in performing risk assessments for drinking-water contaminants (Krishnan and Carrier, 2008, 2013) and used in establishing WHO guidelines for drinking-water quality (WHO, 2017). For instance, in the drinking-water quality guideline for trichloroethylene, the WHO estimated 50% of the TDI as being the allocation factor for drinking water in the total body burden of trichloroethylene, with the remaining 50% coming from inhalation of air and food intake. In the case of chloroform, the WHO estimated 75% of TDI as the allocation factor for ingestion of drinking water, with the remaining 25% coming from inhalation of indoor air (largely due to volatilization from drinking-water) and dermal exposure during showering or bathing.

This consideration of allocations for exposure pathways is an important approach to reducing the total body burden for substances with multiple exposure pathways. However, this approach should be carefully applied only in cases where the target organ and the critical endpoint for inhalation, ingestion, and dermal exposures are the same. Furthermore, it should be based on detailed data for the external exposure allocation and internal absorption, distribution, metabolism, and excretion. This approach is generally applied when the TDI, ADI, standard, or guideline is derived using toxicological data from animals, because the exposure route in the experimental animal study is usually properly controlled. Thus, this approach is not generally applied when these values are derived from human epidemiological data. This is because instances of all exposure during daily activities, including

Table 2
Preliminary exposure assessment and health risk assessment.

Substances	Emission source	Season	*n*	Construction	Maximum indoor air concentration (μg/m^3)	Critical toxic endpoint	Human critical effect level[b] (mg/m^3)	Reference	MOE[a]
2-Ethyl-1-hexanol	hydrolytic degradation of DEHP	2013 summer	93	Existing	133	Eye irritation in humans	NOAEL 8[c] (NOAEL 283)	Kiesswetter et al., (2005) (Klimisch et al., 1998)	60 (2125)
TMPD-MIB	Water-based paint	2012 winter	39	New-built	837	Liver effects in rats	NOAEL 244	O'Donoghue (1984)	292
TMPD-DIB	Water-based paint	2012 winter	39	New-built	661	Liver and renal effects in rats	NOAEL 100	MHW (1993)	151
Ethyl Acetate	Adhesives or paints	2012 summer	93	Existing	203	Degeneration of olfactory epithelium in rats	LOAEL 557	Christoph et al. (2003)	2744
Butyl Acetate	Adhesives or paints	2012 winter	39	New-built	664	Inhibited body weight and neurological effects in rats	NOAEL 1061	David et al. (2001)	1598
PGME	Paints	2012 winter	111	Existing	135	Liver effects in rats	NOAEL 488	Landry et al. (1983)	3615
MMB	Adhesives	2013 summer	93	Existing	93	Liver and renal effects in rats	LOEL 142	OHSC (1976)	1530
DEGME	Paints	2012 winter	39	New-built	337	Overall findings	NOAEL 469	Miller et al. (1985)	1391
DEGEE	Paints	2012 winter	39	New-built	192	Respiratory irritation in rats	NOAEL 40	Hardy et al. (1977)	207
PGMEA	Adhesives or paints	2012 winter	39	New-built	253	Renal effects in rats	NOAEL 716	Miller et al. (1984)	2831
MIBK	Adhesives or paints	2012 winter	39	New-built	151	Renal effects in rats	LOEL 818	Stout et al. (2008)	5417

[a] MOE is calculated from dividing human critical effect level by maximum indoor air concentration.
[b] Human critical effect level is determined from effect level observed in reference and if needed adjusting from discontinuous exposure to continuous exposure (24 h per day, 7 days per week) and adjusting from animal body burden to human equivalent exposure concentration.
[c] NOAEL was revised after discussion on the preliminary risk assessment. Parentheses were values and reference in the preliminary risk assessment. Abbreviations: TMPD-MIB, 2,2,4-trimethyl-1,3-pentanediol monoisobutyrate; TMPD-DIB, 2,2,4-trimethyl-1,3-pentanediol diisobutyrate; PGME, Propylene Glycol Monomethyl Ether; MMB, 3-Methoxy-3-methylbutanol; DEGME, Diethylene Glycol Methyl Ether; DEGEE, Diethylene Glycol Ethyl Ether; PGMEA, Propylene Glycol Monomethyl Ether Acetate; MIBK, Methyl Isobutyl Ketone; DEHP, Di-2-ethylhexyl phthalate; LOEL, lowest-observed effect level; LOAEL, lowest-observed adverse effect level; NOAEL, no-observed adverse effect level; MOE, margin of exposure.

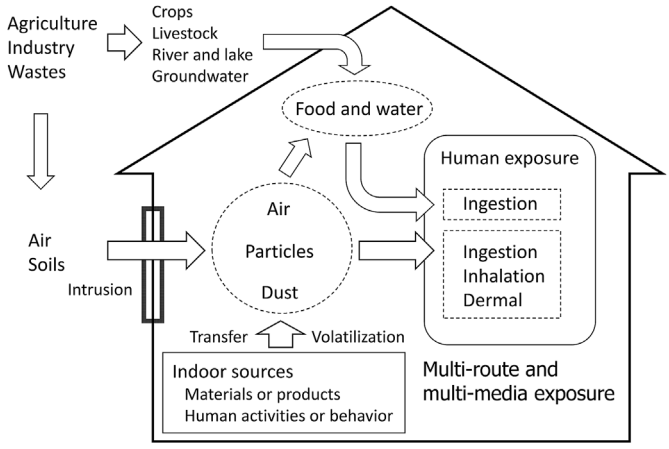

Fig. 2. Pathways to human exposures from sources of SVOCs.

inhalation, ingestion, and dermal exposures, could be spontaneously included in the epidemiological study. However, this approach is needed for epidemiological data from regions where the background levels of exposure are very different. For instance, high-exposure regions and low-exposure regions may have different background levels of food contaminants, affecting the IAQ guidelines for aggregate exposure.

3.2. Multiple exposures to indoor air chemicals (i.e., combined exposure) and the combined health effects

Multiple low-level indoor chemical pollutants are found in indoor environments. Although the indoor air concentration of each pollutant may be low, when many of these pollutants exist collectively in an indoor environment, a greater combined health risk (i.e., additive effects) may be created (Azuma et al., 2016). This situation is defined as combined exposure (Kienzler et al., 2016). The effects of environmental pollutants have been mainly focused on health outcomes from single exposures to single substances, and other multiple risks have been often attributed to confounding in epidemiological studies. However, several epidemiological studies have revealed significant increases in odds ratios for indoor air concentrations that do not exceed IAQ guidelines or reference concentrations (Arif and Shah, 2007; Azuma et al., 2018; Bentayeb et al., 2013; Billionnet et al., 2011; Takigawa et al., 2010; Takigawa et al., 2012). Thus, an approach for evaluating the combined risks of chemical pollutants with similar health effects and future strategies for limiting the total health risk due to multiple low-level indoor chemical pollutants is required.

There are four types of combined effect or interaction: dose addition, response addition, synergism, and antagonism. Since the 1990s, numerous evaluations of combined exposures to mixtures of substances (i.e., food additives, pesticides, veterinary drugs, and contaminants) have been especially undertaken by the Joint FAO/WHO Expert Committee on Food Additives (JEFCA), the Joint FAO/WHO Meeting on Pesticides Residues (JMPR), and the Scientific Committee for Food of the European Commission (subsequently the European Food Safety Authority (EFSA)). Accordingly, group ADI or TDI values have been recommended for several chemical groups as a means to limit their overall intake. For this procedure to be feasible, the substances should have a similar mode of action and a similar range of toxic potency.

An approach that takes account of dose additivity is the toxic equivalency factor (TEF) approach, which scales the exposure for each component of a mixture relative to the potency of an index chemical, such as for dioxins and dioxin-like chemicals (WHO, 2009). Recently, the Panel on Food Contact Materials, Enzymes, and Processing Aids (CEP) of the EFSA has proposed a group TDI of 50 μg/kg bw per day for four phthalates, i.e., di-butyl phthalate (DBP), BBzP, DEHP, and diisononyl phthalate (DINP). The group TDI is based on a plausible common mode of action for the anti-androgenic effect underlying the male reproductive toxicities of these four phthalates (EFSA, 2019a).

The German Committee on Indoor Guide Values (or Ausschuss für Innenraumrichtwerte (AIR)) of the German Environment Agency has established toxicologically based indoor air guide values for over 50 substances or substance groups (Fromme et al., 2019). The AIR defined toluene, ethylbenzene, and xylenes as comprising a group because all C_7–C_8 alkylbenzenes have similar neurotoxic effects. The AIR proposed that, in order to achieve a total evaluation, the ratios of concentrations and guideline values of each compound should be summated, providing a whole sum of risks. The total guideline values are regarded as being complied with if the corresponding sum falls below 1 (AIR, 2016).

This approach also takes into account dose additivity. The concept of dose addition has been the most widely used to determine the common toxic effects of combinations of chemicals (Boobis et al., 2011; EFSA, 2019b; Kortenkamp and Faust, 2018; Meek et al., 2011). This is one approach to assessing the combined risks of pollutants with similar toxicological effects.

Clearly, risks from combined exposure to multiple chemicals as well as methodologies to assess those risks have been discussed, and methodologies and guidance for assessing risks from combined exposure to multiple chemicals have been developed for different regulatory sectors. However, a harmonized, consistent approach for performing mixture risk assessments and management across different regulatory sectors is still lacking (Bopp et al., 2019; Kienzler et al., 2016; Kortenkamp and Faust, 2018; OECD, 2018; Rotter et al., 2018). In particular, related research on indoor chemicals is rare. Given the diversity of possible combinations of chemicals and the diversity of possible approaches, such as those based on use or release, chemical structures, or similar toxicological effects, the application of different approaches and methods can depend on the assessment context and problem formulation. Thus, further research into harmonized approaches to risk assessment of combined exposures to multiple chemicals in indoor environments is needed.

Although health risk assessments based on the measurement of specific pollutant air concentrations have been applied as a means to assess environmental health risks so far, novel approaches to health risk assessment using environmental biomarkers (e.g., sensory irritation markers, central nervous system effect markers, oxidative stress markers, or mutagenic markers, which directly represent health stress due to environmental factors) to evaluate biological and health effects are required to replace existing health risk assessment methods. This approach will prevent negative health effects caused by combined exposure to multiple low-level pollutants and/or exposure to alternative chemicals that potentially pose the risk of impairing human health.

4. Concluding remarks and future perspectives

IAQ guidelines have been established and continue to be refined based on the fundamental concept that, in order to protect public health, unnecessary exposure to indoor chemicals should be minimized and chemicals should be safely and appropriately used so that they have no adverse effects on human health. The types and concentrations of indoor chemicals have shifted over time due to lifestyle changes and the development of novel household products and building materials. Therefore, the continued monitoring of indoor chemicals and the development of IAQ guidelines for substances that present potentially high health risks are essential for ensuring public health. Moreover, in indoor environments, there are multiple media by which humans come in contact with indoor chemicals and multiple exposure pathways that can affect human health, particularly for SVOCs. Furthermore, combined exposure to multiple low-level chemical pollutants occurs in indoor environments. Therefore, development of an integrated multi-pollutant and multicompartmental approach for limiting aggregate and combined exposures is essential in order to determine the extent of

threats to public health posed by indoor chemicals. Developing approaches to assess health risks using environmental biomarkers that directly represent health stress due to environmental factors will be required as the future approach to prevent negative health effects caused by combined exposures to multiple low-level pollutants.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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