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REVIEW ARTICLE

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Comprehensive review of 2-ethyl-1-hexanol as an indoor air pollutant

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Abstract

Objectives: 2-Ethyl-1-hexanol (2EH), a fragrance ingredient and a raw material for the production of plasticizer di(2-ethylhexyl) phthalate, is responsible for sick building syndrome (SBS). This review aims to clarify the 2EH characteristics as an indoor air pollutant such as indoor air concentration, emission mechanism, toxicity, and clinical effects.

Methods: Scientific publications in English that has been made available on PubMed as of June 2018 and ad hoc publications in regional languages were reviewed.

Results: Inhalation exposure to 2EH caused mucous membrane irritation in the eyes, nose, and throat in experimental animals. Studies in human volunteers revealed an increase in olfactory irritation and eye discomfort. There has been increasing evidence of 2EH being present in indoor air in buildings. The primary sources of 2EH emissions are not building materials themselves, but instead the hydrolysis of plasticizers and flooring adhesives. In particular, compounds like di(2-ethylhexyl) phthalate present in polyvinyl chloride flooring materials are hydrolyzed upon contact with alkaline moisture-containing concrete floors. That being said, it may be observed that indoor concentrations of 2EH increased every year during summer.

Conclusions: Unlike other volatile organic compounds that cause SBS, 2EH can be retained in indoor air for long durations, increasing the likelihood of causing undesirable health effects in building occupants exposed to it. As a precautionary measure, it is important to use flooring materials that do not emit 2EH by hydrolysis, or to dry concrete before covering with flooring materials.

KEYWORDS

2-ethyl-1-hexanol, emission mechanism, indoor air pollution, indoor concentration, sick building syndrome, volatile organic compounds

1 | INTRODUCTION

Indoor air pollution triggers symptoms of irritation, such as dryness in the skin and eyes, and pain in the nose and throat. It also causes psychoneurotic symptoms, such as dizziness, nausea, and headache. These symptoms, which are common among occupants of nonindustrial buildings such as offices and schools, have been defined as sick building syndrome (SBS). This syndrome is caused by chemical factors such as formaldehyde and other volatile organic compounds (VOCs),[1,2] biological factors such as mold and tick,[3,4] or physical factors such as temperature and humidity.[5,6] In

recent years, the VOC 2-ethyl-1-hexanol (2EH) (CAS No. 104-76-7) has drawn attention as one of the prominent causes of SBS.[7]

2-Ethyl-1-hexanol is used mainly as a raw material for the production of di(2-ethylhexyl) phthalate (DEHP), a plasticizer for polyvinyl chloride (PVC), and as a fragrance component in cosmetics,[8] but is hardly detected in outdoor environments. 2EH is a known metabolite of the plasticizer DEHP, a hepatic carcinogen in rodents.[9] Based on a long-term study in rats in which the no-observed-effect level (NOEL) of 2EH was found to be 50 mg/kg/bw/day with a safety factor of 100, the acceptable daily intake (ADI) of 2EH in humans was established as 0-0.5 mg/kg body weight by the Joint Food and Agriculture Organization-World Health Organization Expert Committee on Food Additives.[10]

It was reported that 2EH is detected at high concentrations in buildings where occupants complained of SBS symptoms.[7] Mucosal irritation in the eyes and nose were reported as the primary endpoints in studies examining the effects of 2EH exposure in humans and animals.[11,12] However, this compound may also affect human health at low concentrations. The recommended 8-hour time-weighted average occupational exposure limit of 2EH is 5.3 mg/m^3 (1 ppm) in Europe[13] and Japan.[14] On the other hand, the preliminary reference concentration of 2EH concentration in general indoor environments is 0.1 mg/m^3, same as the Guide Value I (precautionary value) in Germany.[15] The reference concentration for general environment is also being considered in Japan.[16]

An important characteristic of 2EH as an indoor air pollutant is the seasonal fluctuation of its indoor air concentration; it is detected at higher concentrations in high-temperature and humid seasons and at markedly lower concentrations during winter.[17,18] Therefore, unless appropriate countermeasures are taken to reduce 2EH emissions, its indoor air concentration will periodically be high, which could cause long-term exposure to 2EH in people exposed to high indoor concentrations of 2EH.[19]

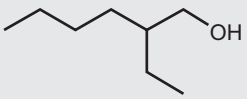
Risk assessment studies have reported several effects of oral[20-22] and inhalation exposure[23,24] to 2EH in animals. However, these effects, along with other characteristics of 2EH as an indoor air pollutant, have not been summarized in any comprehensive review. Therefore, this review aims to summarize current findings of relevant publications on the indoor air concentration, emission mechanism, toxicity, and clinical effects of 2EH.

We reviewed literature in English that has been made available on PubMed and Google Scholar as of June 2018 and ad hoc publications in regional languages. We searched papers with the term "2-ethyl-1-hexanol" and chose the literature were related to indoor air pollutant and toxicity.

2 | PHYSICAL PROPERTIES AND USE OF 2EH

The physical and chemical properties of 2EH are summarized inTable 1. There are many household products

TABLE 1 The physical and chemical properties of 2EH

Property	Value	Reference
Molecular formula	$C_8H_{18}O$	-
Structure formula		-
CAS No.	104-76-7	-
Molecular weight	130.23 g/mol	-
Physical form	Colorless, oily liquid with mild, sweat, and slightly floral-rosy odor	8
Melting point	-75°C	26
Boiling point	188.52°C	8
Density at 20°C	0.834 g/cm^3	8
Vapor density	4.49 g/cm^3	26
Vapor pressure	0.06 mmHg at 20°C, 0.185 mmHg at 25°C	8
Solubility	Soluble in organic solvents	27
Solubility in water	880 mg/L at 25°C, 1000 mg/L at 20°C	27
Odor threshold	0.075 ppm (perception), 0.138 ppm (100% recognition)	27
Conversion factors for vapor (25°C 1013 hPa)	1 ppm = 5.32 mg/m^3	25

manufactured using 2EH. The plasticizers DEHP and di(2-ethylhexyl) adipate (DEHA), used in the processing of plastic and rubber, are produced with 2EH as a raw material. 2EH is also used as a raw material for the production of 2-ethylhexyl acrylate, an adhesive component, and as a fragrance ingredient in decorative cosmetics, fine fragrances, toiletries (such as shampoos and soaps), and non-cosmetic products, such as household cleaners and detergents.[8] In the environment, 2EH is volatilized from soil or water surfaces into the atmosphere.[25]

3 | TOXICOKINETICS OF 2EH

2-Ethyl-1-hexanol is absorbed by the gastrointestinal tract and skin. Alcohol dehydrogenase (ADH) rapidly oxidizes the hydroxyl group in 2EH, forming 2-ethyl-1-hexanal. It is further oxidized by aldehyde dehydrogenase (ALDH), forming 2-ethyl-1-hexanoic acid (2EHA), which is excreted mainly as a glucuronate conjugate in urine. ADH activity for 2EH was reported to be 8.6 nmol/mg/min and 4.2 nmol/mg/min in humans and mice, respectively. Furthermore, ALDH activity for 2EH was 3.6 nmol/mg/min and 5.6 nmol/mg/min in humans and mice, respectively.[28]

Within 24 hours of orally administrating 2EH at 8.3 mmol/kg, 86.9% of the compound was excreted in urine as the glucuronide conjugate metabolite.[29,30]

Following oral administration at doses of up to 300 mg/kg, 2EH was efficiently absorbed in male CD rats. Within 28 hours, 2EH metabolite was excreted in exhaled breath (as CO_2; 6%-7%), feces (8%-9%), and urine (80%-82%). The major urinary metabolite of 2EH was 2EHA, generated by decarboxylation of partially β-oxidized 2EH. The other identified metabolites were 2-ethyl-5-hydroxyhexanoic acid, 2-ethyl-5-ketohexanoic acid, and 2-ethyl-1,6-hexanedioic acid. Almost all (96.1%) of the administered 2EH was excreted as a metabolite and only approximately 3% was excreted unchanged.[31]

In another study, dermal administration of 2EH at 1 g/kg resulted in only 5% of the compound being absorbed at a rate of 0.57 mg/cm^2/h.[32] In a comparative study, the percutaneous absorption rates of 2EH in male rats and humans were 0.22 mg/cm^2/h and 0.038 mg/cm^2/h, respectively, with a (rat/human) ratio of 5.78.[33] 2EH was detected in the exhaled breath at 4 μg/m^3 (0.0008 ppm).[34] 2EH was also detected on the skin surface.[35] The concentration of 2EH gas released from the hand skin was 39.9-136.2 μg/m^3 (7.7-25.6 ppb).[36] Moreover, 2EH was considerably more abundant in the stool of neonates than adults, suggesting that neonates may be more susceptible to risks from exposure than adults to plastic materials containing plasticizers.[37]

4 | EXPOSURE SCENARIO

4.1 | Sources of 2EH Emissions

The general population may be exposed to 2EH from inhalation of ambient air, ingestion of food and drinking water, or dermal absorption of this compound or other products containing 2EH.[25] Studies have reported 2EH emission from various sources, such as carpets,[38,39] furnitures,[40] computers,[41] books,[42,43] and food wrappings.[44] Building materials, such as insulation and gypsum board,[45] wallpaper,[46] paint,[47] PVC flooring,[48] and adhesives,[49] are also sources of 2EH emissions.

Several reports point out that flooring is a prominent source of 2EH air pollution in buildings. The region of the highest 2EH concentrations in apartment houses was concrete slabs surface, which was directly in contact with a vinyl carpet.[50] In a school conference room with a 2EH air concentration of 1902 μg/m^3, the rates of 2EH emission from the carpet tile and concrete surface beneath the carpet were 2492 μg/h/m^2 and 12,697 μg/h/m^2, respectively, measured using the double-cylinder chamber method.[51] It was also reported that 2EH concentrations in the air increased with the amount of 2EH emitted from the floor.[52] In a study investigating VOC emission using a field and laboratory emission cell (FLEC) method, 2EH was found to be 47%-76% of the total VOCs emitted from the floor coverings.[53] 2EH was emitted from the surface of a concrete floor after its PVC floor covering was removed.[54] One study revealed that 2EH emission by a PVC flooring material decreased over time during the 60-day experiment,[55] which contradicted findings from a different study which found that 2EH indoor concentration fluctuated over a long period of time—increasing in summer when the temperature rose and decreasing in winter when the temperature fell.[17,18] Therefore, in addition to primary 2EH emission by the 2EH-containing products, other emission mechanisms should also be considered. Some of these mechanisms have been identified and are described in the next section.

4.2 | Emission of 2EH from hydrolysis reaction

A study showed that 2EH is generated from hydrolysis of DEHP in an environment simulating a concrete slab with a relative humidity (RH) between 70% and 100% and pH between 11 and 13. In the study, DEHP hydrolysis and 2EH emission increased with an increase in pH.[56] Since DEHP has a half-life of 100 years at pH 8 and 30°C,[57] it is hardly degraded under normal indoor environment. Additionally, DEHP on the surface of cement with higher moisture content emits higher amount of 2EH.[58] Thus, there is very little doubt that the amount of 2EH emission by DEHP is related to the moisture content of the cement with which it has direct contact.[51] Therefore, dampness seems to play a major

role in determining the amount of 2EH emitted. A study examined the relationship between RH and 2EH indoor air concentration, and showed that in buildings with RH values of 58%-75% and 21%-22%, the 2EH indoor air concentrations are 9 μg/m^3 and 3 μg/m^3, respectively.[59] Additionally, in a room with high amount of 2EH emission, the moisture content of its concrete floor was as high as 8.2%.[51] Using the FLEC method, 2EH was detected after PVC flooring was directly attached to a concrete floor[60] or after PVC flooring material was tightly attached to a self-leveling (SL) material.[51] The amount of 2EH emission increases as the moisture content of an SL material increases.[61] Taken together, long-term emission of 2EH can be attributed to the hydrolysis of DEHP contained in the flooring material,[49] supported by the fact that 2EH concentration in the air decreases significantly after plastic coverings, adhesives, and leveling layers are removed from the floor, all while the rooms were warmed to 55°C and simultaneously ventilated by additional exhaust fans for a week.[53]

Several published studies have reported on various materials that emit 2EH.[18,62,63] We postulated, based on the amount of 2EH emission from flooring that compounds containing a 2-ethyl-1-hexyl moiety, such as DEHP contained in PVC, and 2-ethylhexyl acrylate contained in adhesives, are hydrolyzed to emit 2EH when the backing of carpeting material was in contact with concrete floors.[18,51] At pH values 11 and 13, flooring materials composed of DEHP-containing PVC and 2-ethylhexyl acrylate-containing adhesives emitted a large amount of 2EH. Additionally, adhesives that did not contain 2-ethylhexyl acrylate also emitted 2EH when combined with PVC flooring, but did not when combined with linoleum flooring.[64] These results confirmed our postulate that a contact between a compound having a 2-ethylhexyl group and a concrete floor causes secondary emission of 2EH from a hydrolysis reaction (Figure 1), which seems to be dependent on the pH and moisture content of the concrete surface. A similar emission of n-butanol and 2-butanol from hydrolysis reaction can be observed.[65,66] It is theorized that moisture in concrete is retained when the concrete is covering with a flooring material. Consequently, the amount of 2EH emitted increases in summer when the temperature rises and decreases in winter when the temperature drops. As this cycle repeats itself over a long period of time, 2EH will continue to be emitted, making it theoretically impossible to altogether prevent gradual and prolonged 2EH emission by ventilation and bakeout. In order to fundamentally eliminate the problem associated with 2EH emission, it is necessary to thoroughly dry concrete before covering it with a flooring material.

4.3 | Emission of 2EH by microbiological reaction

It has been reported that some microorganisms in gypsum board or walls of a flood-damaged house emit 2EH.[67,68] *Aspergillus versicolor,* which can grow on rich malt extract medium and several synthetic media, also emits 2EH.[69] When cultivated in indoor dust for 7 days at an RH of 84%-86%, and 2 days at an RH of 96%-98%, *A. versicolor* generated several microbial VOCs, including 2EH, by metabolizing various hydrocarbons and fatty acids contained in the dust.[70] Furthermore, *Rhodococcus rhodochrous* was reported to decompose the plasticizers DEHA[71] and DEHP,[72] thereby generating 2EH. *Mycobacterium* sp. also decomposes DEHP to produce 2EH.[73] A pathway of 2EH production through the biological degradation of DEHP and DEHA has been proposed.[74] Taken together, microorganisms

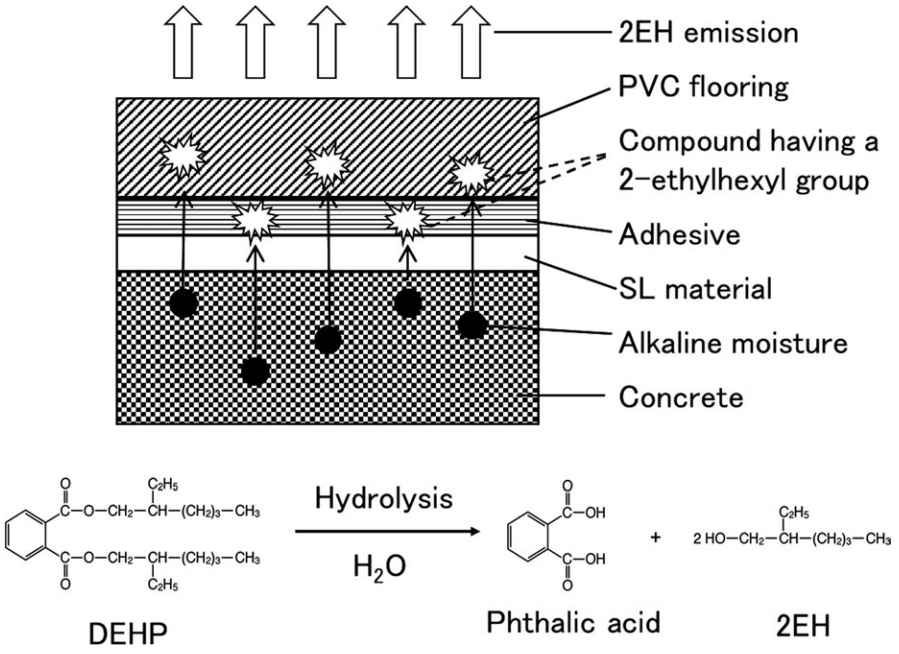


FIGURE 1 The emission mechanism of 2-Ethyl-1-hexanol (2EH) by a hydrolysis reaction. Compounds having 2-ethylhexyl group contained in floor materials and adhesives are hydrolyzed by the alkaline moisture content in concrete. For example, DEHP contained in PVC flooring is hydrolyzed, emitting 2EH into the room[18]

have also been related to 2EH emission. In fact, several studies claim that 2EH in indoor air is a product of the decomposition of plasticizers by microorganisms.[75] That said, all evidence in those studies were limited to in vitro findings. Therefore, the contribution of microbiological decomposition of plasticizers to 2EH indoor air concentration is still unverified. Detailed investigations are required.

5 | INDOOR CONCENTRATIONS OF 2EH

2-Ethyl-1-hexanol has been reported in the indoor air of buildings, mainly in Japan, Northern Europe, and North America (Table 2). High level of 2EH concentration has become a particular problem in a newly constructed university building in Japan, where 2EH concentrations were 1086 μg/m^3 and 1183 μg/m^3.[7,18] A study in Sweden reported that concentrations of 2EH up to 1000 μg/m^3 were detected in offices.[76] Two reports that measured the concentration of 2EH in North America showed 0.3-48 μg/m^3 and <7.95 μg/m^3.[77,78]

2-Ethyl-1-hexanol was detected in 92 out of 99 rooms in the 42 buildings studied, with an average indoor concentration of 16.5 μg/m^3 compared to an outdoor 2EH concentration of 1.9 μg/m^3.[19] In a survey of 175 rooms such as offices, sales floor, and classrooms in 57 buildings that were no older than 1 year, 2EH was detected in 99% of the rooms, with an average indoor concentration of 13.5 μg/m^3.[79]

2-Ethyl-1-hexanol has also been detected in other university building, school, shopping centers, and museums.[80-83] Furthermore, 2EH was detected in the living rooms at a maximum indoor concentration of 5.1 μg/m^3.[84] In another study, the 2EH indoor concentrations in 150 rooms of an apartment building were 1-86 μg/m^3.[50] In Germany, the average 2EH concentration in 230 houses was 2 μg/m^3 (<0.1-10 μg/m^3).[25]

The geometric mean of 2EH concentration was significantly higher in samples collected in summer (55.4 μg/m^3) than in those collected during winter (13.7 μg/m^3) ($P < 0.01$).[56] Several similar trends have been reported.[85,86]

TABLE 2 Summary of indoor air concentration of 2-Ethyl-1-hexanol

Country	Location	Study period	Concentration (μg/m^3)	Reference
Japan	University	March 2001	164-1086	7
Japan	University	Summer 2002	25-1183	18
Sweden	Office building	Not reported	1000 (max)	74
Japan	Nondomestic buildings	June 2002-October 2004	16.5 (geometric mean)	19
USA	Office building	Summer 1995 Winter 1997-1998	0.3-48	77
USA	Houses	1997-1998	<7.95	78
Japan	Large-scale buildings	2003-2007	13.5 (geometric mean)	79
Japan	University	August-September 2003	132 (max)	80
Japan	School	August 2007	12-302	81
Japan	Shopping center	June 2006	69.2 (max), 6.2 (geometric mean)	82
Japan	Museums	September and October 2005	1.30 (max)	83
Japan	Dwellings	October 2013 and January 2014	5.1 (max)	84
Sweden	Residential buildings	Not reported	1-86	50
West Germany	Dwellings	Not reported	2 (average)	25
Japan	Large-scale buildings	July 2004-September 2007	Summer 55.4, winter 13.7 (geometric mean)	17
Switzerland	University	January and June 2000	4-17	85
Europe	Buildings	Summer 2012-winter 2013	Summer 4.7, winter 3.9 (average)	86
Finland	Office building	December 2000-March 2001	ca. 100	53
Sweden	Buildings	Not reported	17 (max), 9.8 (average)	87
Sweden	Rehabilitation center	Not reported	0.3-0.6	88
Japan	Temporally houses	June 2011	69 ± 12.8	89
Sweden	Hospitals	November 1996-January 1997	4.8-19.8	90
Sweden	Hospitals	January-February 1997	5-20	91
Sweden	Hospitals	January-February 1997	2-32	92

With regard to building conditions that could facilitate 2EH emission, a damp office building had a higher 2EH concentration than a dry office building.[53,87] A rehabilitation center with wet linoleum flooring materials had 2EH concentrations of 0.3-0.6 μg/m^3.[88] A survey conducted in five temporary houses that used PVC flooring materials showed a 2EH indoor concentration of 69 ± 12.8 μg/m^3.[89] Furthermore, three surveys were conducted in the same four geriatric hospital buildings, which were of various ages. 2EH was detected in two buildings aged 3 and 11 years with PVC floorings and dampness.[90-92] On the other hand, the two other buildings, aged 1 and 71 years, showed no sign of dampness and had 2EH concentrations below the detection limit (<1 μg/m^3).

Thus, it was concluded from these studies that 2EH concentration is not related to the age of buildings. Rather, the use of PVC, the dampness and higher temperature are known to contribute to 2EH emission. The reason it was detected frequently and at such high concentrations in Japan has not been clarified.

6 | EFFECTS ON HUMAN HEALTH

6.1 | Environmental exposure

A summary of 2EH effects on human health is presented inTable 3. Increased occurrence of ocular and nasal symptoms was observed in subjects working in buildings where 2EH was detected at levels between 5 and 20 μg/m^3.[91] Asthma symptoms may occur due to the humidity in concrete floor constructions that affect 2EH emission.[92] In a humid building where people developed nasal mucosal inflammation, it was observed that fungi and bacteria were also abundant, wherein average 2EH concentration was 9.8 μg/m^3.[87]

At a university in Japan, where 2EH concentration was 1086 μg/m^3 in maximum, a case of a female professor who complained of coughing, throat irritation, and sore eyes was reported. 2EH was detected at a prominently high concentration of 408-1866 μg/m^3. Other staff members also complained of area-associated SBS symptoms in rooms where 2EH concentrations were higher than 160 μg/m^3.[7] In comparison with the SBS symptom prevalence, there was no significant difference between classrooms where 2EH concentration reached 65.5 μg/m^3 and 4.8 μg/m^3. However, symptoms of the nose, throat, and lower respiratory tract were observed only in rooms with high 2EH concentrations.[18] Faculty members who used a conference room with 2EH concentration of over 336 μg/m^3 showed a high prevalence of such complaints.[7] Therefore, it was estimated that the threshold at which symptoms appeared excessively in a population should be in the range of 65.5-336 μg/m^3.[18]

In Finland, several respiratory and dermal symptoms and irritation in the eyes were reported in environments with 2EH concentration of 1-4 μg/m^3.[53,54]

In a rehabilitation center in Sweden, where airborne concentrations of 2EH were very low (0.3-0.6 μg/m^3), the staff who had been previously exposed to VOCs as well as 2EH developed SBS symptoms after 2 days of re-exposure regardless of a 4-month period without VOC exposure.[88]

In a newly built university building in Japan, as the indoor concentration of 2EH decreased by ventilation, the number of occupants who complained about headache and eye irritations decreased.[93]

At a technical university in Switzerland, employees and students had complained about deteriorated indoor air quality after the building was renovated. Some employees even suffered from sickness and headache. Indoor concentration of 2EH was 4-17 μg/m^3.[85]

As described above, there are reports which claim that 2EH is present indoors, even in a general living environment,

TABLE 3 Summary of effects on human health

Country	Location	Symptoms	Concentration (μg/m^3)	Reference
Sweden	Hospital	Nasal and ocular symptoms	5-20	91
Sweden	Hospital	Asthma symptoms	2-32	92
Sweden	Building	Nasal mucosal inflammation	9.8 (average), 17 (max)	87
Japan	University	Coughing, throat irritation, and sore eyes	164-1086	7
Japan	University	Problems with the nasal passages, throat, and lower airways	25-1183	62
Finland	Office building	Respiratory, conjunctival, and dermal symptoms; adult-onset asthma was approximately nine times higher	Mean 2 (range 1-3)	53
Finland	School	Irritation symptoms in the respiratory tract and eyes	1-4	54
Sweden	Rehabilitation center	Ocular, nasal, and respiratory symptoms	0.3-0.6	88
Japan	University	Ocular pain and headache	37.1-62.1	93
Switzerland	University	Sickness and headache	4-17	85

possibly causing irritation and inflammation in the mucous membranes of the respiratory tract and nasal cavity. However, the dose-response relationship and the discrepancy in the lowest-observed-adverse-effect-level (LOAEL) among the countries remain to be further clarified.

6.2 | Experimental inhalation or topical exposure settings

To assess the acute effects of 2EH, volunteers were exposed to 2EH vapor (1 mg/m^3) for 2 hours. During exposure, the volunteers reported a significant increase in nasal and eye discomfort. No differences in response were observed between the sexes, or between the atopic and nonatopic treatments.[94]

Twenty-four young men were assessed before, during, and after the 4-hour exposure. As 2EH concentration increased in three levels, 8.14, 56.6, and 116 mg/m^3, nasal flow reduction and substance P concentration were increased.[95]

To evaluate the effect of 2EH on sensory irritation, 2EH at mean concentrations of 1.5, 10, and 20 ppm (7.98, 53.2, and 106 mg/m^3, respectively) were used for either constant or variable for the 4-hour exposure. The study revealed a strong dose-response relationship between the concentration of the airborne solvent and blinking rate. The study suggested a critical dose for 1-hour constant exposure lied between 10 and 20 ppm, and the LOAEL for eye irritation due to 4-hour exposure was 10 ppm under variable concentration conditions at a peak concentration of 20 ppm.[12]

TABLE 4 Summary of inhalation and oral exposure

Concentration/dose	Period	Exposure	Species	Effects	Reference
227 ppm	6 h	Inhalation	Mouse, rat, and guinea pig	Mucous irritation in the eyes, nose, throat, and respiratory passages	11
0, 15, 40, 120 ppm	90 d	6 h/d Inhalation	Rat	NOAEL of 120 ppm	23
0, 20, 60, 150 ppm	3 mo	8 h/d Inhalation	Mouse	Inflammation and degeneration of the olfactory epithelium at ≥20 ppm	24
100 mg/kg	Single	Intragastric administration	Rat	No direct effect on protein kinase C activity	107
3.8 mmol/kg/d	3 d	Gastric intubation	Rat	Increased cytochrome P450 4A1 levels	108
2% (20 mg/kg/d)	3 wk	In food	Rat	Significant decreases in triglyceride and cholesterol serum levels	109
88 g/d/hen	Single	In food	Hen	Lowered plasma level of free cholesterols, reduced liver fats	110
833 mg/kg/d	3 wk	Gastric intubation	Rat	Increased liver weight	111
4 mmol/kg/d (520.8 mg/kg/d)	7 d	Gavage	Rat	Increases in both wet liver weight and antipyrine clearance	112
1000 mg/kg/d	3 wk	Gavage	Rat	Thirty percent increase in liver-to-body weight ratio; increase in peroxisome cell fraction and in peroxisome density	22
130 mg/kg/d	14 d	Gavage	Rat	Not induce hepatomegaly, peroxisome proliferation, and hyperlipidemia	113
0-1.75 g/kg/d	14 d	Gavage	Mouse, rat	Increases in relative liver weights and peroxisomal β-oxidation	114
0, 25, 125, 250, 500 mg/kg/d (5 consecutive days/wk)	13 wk	Gavage	Mouse, rat	Reduced body weight gain and increased relative liver, kidney, stomach, and testes weights at 500 mg/kg/d NOEL of 125 mg/kg/d	20
0, 50, 200, 750 mg/kg/d (5 consecutive days/wk)	18 mo	Gavage	Mouse, rat	Reduced body weight gain and increased relative liver and stomach weights at 500 mg/kg/d	21
0, 50, 150, 500 mg/kg/d (5 consecutive days/wk)	24 mo	Gavage	Rat	Decrease in body weight gain and dose-dependent increases in relative liver, stomach, brain, kidney, and testis weights at 150 mg/kg/d and 500 mg/kg/d	21

Experiments with human volunteers at three time-weighted average 2EH concentrations (1.5, 10, and 20 ppm) were performed for 4 hours under conditions of either constant or variable concentrations. At 10 ppm, nasal irritation increased with time, and 20 ppm resulted in remarkable irritation. Additionally, attention reduction was considered to occur around 20 ppm. Therefore, the LOAEL for irritability and nasal irritation was 10 ppm. Olfactory- and trigeminal-mediated symptoms and intensities of odor, eye, and nasal irritations showed a dose-dependent response. Over the course of the 4-hour exposure, only olfactory symptoms decreased, while nasal irritations remained nearly unchanged and eye irritations slightly increased.[96,97]

With regard to skin sensitization to 2EH, a maximization test was carried out on 29 volunteers. Tested at 4% in petrolatum, 2EH produced no irritation or sensitization after 48 hours in a closed-patch test on human subjects.[98]

7 | IN VIVO EFFECTS ON ANIMALS

7.1 | Inhalation exposure

The effects of 2EH inhalation on animals are summarized in Table 4. Inhalable 2EH at 1210 mg/m^3 (227 ppm) was administered by a single 6-hour inhalation exposure to groups of Swiss mice, Wistar rats, and English Short Hair guinea pigs. 2EH-induced local irritation was occurred in the mucous membranes of the eyes, nose, throat, and respiratory tract. However, these responses were temporary, and all animals had recovered within an hour of terminating exposure.[11] In another study, mice exposed to 2EH at 234 mg/m^3 (44 ppm) by inhalation exhibited a decrease in respiratory rate (RD_{50}) by 50%.[99]

A 90-day subchronic inhalation toxicity study of 2EH was performed in Wistar rats. In total, 10 males and 10 females per group were exposed to 2EH vapors at concentrations of 15, 40, and 120 ppm for 6 hours/day over a 90-day period. No 2EH-related adverse effects were observed. The highest concentration tested under these conditions (120 ppm) was described as the no-observed-adverse-effect-level (NOAEL) of 2EH in both male and female rats.[23]

Male ICR mice were exposed to 0, 20, 60, or 150 ppm 2EH for 8 hours/day each week, 5 days every week over 3-month period. After a week of exposure to 2EH, the mice showed inflammation and degeneration in the olfactory epithelium, and mice exposed to 2EH at ≥20 ppm showed a significant concentration-dependent reduction in the number of olfactory receptor neurons and globose basal cells. The olfactory bulb showed a reduction in the diameter of glomeruli and in the number of olfactory nerves at 3 months. These histopathology data suggested that 2EH has persistent effects on the olfactory system.[24]

7.2 | Oral exposure

The effects of 2EH oral exposure on animals are summarized in Table 4. The acute oral lethal dose 50% (LD_{50}) of 2EH in rats were reported to be 3.3 g/kg,[100] 2.05 (range 1.52-2.77) g/kg,[101] 2.46 g/kg,[102] 7.1 (range 5.5-9.1) g/kg,[103] 3.2 g/kg,[104] 3.29 (range 2.87-3.79) g/kg,[105] and 3.73 g/kg,[11] whereas in mice it was reported to be 2.500 g/kg.[106]

A tumorigenic effect of 2EH was examined by determining its effect on protein kinase C activity. It was revealed that 2EH exerted no direct effect on protein kinase C activity in vivo.[107]

In another study, Wistar rats were treated with 2EH at 494 mg/kg by gastric intubation once a day for 3 days. At 24 hours after the last dose, the level of cytochrome P450 4A1, activity of lauric acid ω-hydroxylase and palmitoyl-CoA oxidase in the rats were increased. However, 2EH did not alter the activity of lauric acid (ω-1)-hydroxylase.[108]

Male Fischer 344 rats were fed diets containing 2EH at 20 mg/kg/day for 3 weeks, and significant decreases in the levels of serum triglyceride and cholesterol were observed.[109]

In laying hens, the diet which contained 2% (88 g/day/hen) 2EH lowered the plasma level of free cholesterols, liver fats but not significantly alter liver weight.[110]

Other studies using rats revealed that 2EH increase liver weight,[111] antipyrine clearance,[112] and peroxisome cell fraction.[22]

Male rats were administered with 2EH (1 mmol/kg/day) for 14 days. This treatment did not induce hepatomegaly, peroxisome proliferation, and hyperlipidemia in the rats.[113]

Male and female rats (Wistar- and Fischer 344-derived) were orally administered with 2EH for 14 consecutive days. At doses above 1.05 g/kg/day, 2EH was toxic, and resulted in their death. Relative liver weights (liver-to-body weight ratios) administered at above 0.70 g/kg/day were increased in a dose-dependent manner.[114]

2-Ethyl-1-hexanol was administered by oral gavage to male and female Fischer 344 rats and B6C3F1 mice (0, 25, 125, 250, and 500 mg/kg/day) for 13 weeks. In the rats, 500 mg/kg/day reduced body weight gain, increased relative liver, kidney, stomach, and testes weights, and moderate changes at gross and microscopic levels in the liver and forestomach were observed. In the mice, 2EH at 500 mg/kg/day increased relative stomach weights in males and produced few gross and microscopic changes in the forestomach and liver (female). A NOEL of 125 mg/kg/day was established for 2EH in rats and mice.[20]

2-Ethyl-1-hexanol at 0, 50, 200, and 750 mg/kg were administered to mice five times a week for 18 months. At 750 mg/kg, a slight increase in non-neoplastic focal hyperplasia in the forestomach vs vehicle controls was shown. Besides, relative liver and stomach weights and incidence

of hepatocellular carcinomas were increased. No metastases were observed.[21]

The authors also reported the chronic effects in rats treated with 0, 50, 150, and 500 mg/kg 2EH by gavage five times a week for 24 months. Reduced body weight gain with 2EH at above 150 mg/kg and an increased incidence of lethargy and unkemptness were observed at 50 mg/kg. There were dose-related increases in relative liver, stomach, brain, kidney, and testis weights. Apart from marked aspiration-induced bronchopneumonia in rats at 500 mg/kg, the hematologic, gross, and microscopic changes indicative of tumors were comparable among all rat groups.[21]

7.3 | Topical exposure

The acute dermal LD_{50} value was 2.38 (1.51-2.76) g/kg[102] in rats, over 2.6 g/kg[11] in rabbits. Signs of percutaneous toxicity were not observed, and skin irritation was moderate when 2EH (at 0.10, 0.316, 1.00, and 3.16 ml/kg) was dermally administered to the closely clipped, intact abdominal skin of albino rabbits.[11] Additionally, 2EH was administered to rabbit eyes and the subsequent corneal injury was graded as 5 on a scale of 10,[102,115] indicating severe acute eye irritation.[11]

2-Ethyl-1-hexanol diluted by polyethylene glycol (1%, 3%, 10%, 30%, and 100%) was administered to rabbit eyes. The potent ocular irritant 2EH produced moderate eye irritation from concentrations between 3% and 30%, and severe eye irritation at 100%.[116]

7.4 | Intraperitoneal exposure

Intraperitoneal treatment of rats with 0.32 g/kg 2EH decreased plasma ketone bodies (from 0.8 to 1.6 mmol/L), increased hepatic triglycerides, and increased lipids predominantly in periportal regions of the liver lobule.[117]

After intraperitoneal injection, 2EH did not induce a significant production of hydrogen peroxide generated by peroxisome proliferators in the rat hepatocytes.[118]

8 | EFFECTS ON REPRODUCTION AND TESTIS

Since there is no report in humans regarding reproductive toxicity effects, Japan Society for Occupational Health classified 2EH as group 3: Substances suspected to cause reproductive toxicity, based on the animal experimental data showing the effects on fetal growth and skeleton formation.[14]

Sprague-Dawley rats were exposed to 2EH vapor for 7 hours/day on gestational days (GD) 1-19 at 850 mg/m^3 (160 ppm). 2EH reduced maternal food intake, but there were no significant decreases in weight gain, water intake, number of fetuses, and fetal weight.[119]

Teratological studies were conducted using Wistar rats orally treated with 2EH at up to 1660 mg/kg on GD 12. Teratogenic fetal malformation was increased,[120] but there was no clear description in the article whether an appropriate comparison with the control group was made or not.

Developmental effects of 2EH in Wistar rats at 0, 130, 650 and 1300 mg/kg (10 animals per group) by gavage, from GD 6 to 15, were investigated. 2EH showed significant maternal toxicity with autopsy effects at 1300 mg/kg and six animals were found dead on GD 9, 10 and 13. In this group, there was also an increased number of early resorptions and high post-implantation loss. The mean fetal body weight markedly decreased and an increased frequency of fetuses with malformations was observed. Furthermore, the number of fetuses bearing skeletal variations, retardations and dilated renal pelvis increased. A 650 mg/kg dose of 2EH showed slight clinical signs/symptoms in the mother without maternal body weight changes. Fetal body weights were slightly reduced, and the number of fetuses with skeletal variations and retardations increased. Six fetuses among the three litters in this group showed asymmetric dumbbell-shaped thoracic vertebrae. The NOAEL for the maternal and fetuses was 130 mg/kg.[121]

2-Ethyl-1-hexanol was orally administered to female mice at 1525 mg/kg/day from GD 6 to 15. Of 49 maternal mice, 17 died, and maternal body weight decreased. In addition, the number of births, the survival rate, and the weight of the infant significantly decreased.[122]

2-Ethyl-1-hexanol was administered via occluded dermal application for 6 hours/day on GD 6 through 15 to pregnant Fischer 344 rats at 0-2520 mg/kg/day. The NOAEL for the maternal toxicity of 2EH was 252 mg/kg/day based on skin irritation, and 840 mg/kg/day based on systemic toxicity. The NOAEL for developmental toxicity was at least 2520 mg/kg/day, with no teratogenicity.[123]

The rate of Sertoli cell proliferation was assessed in male CD Sprague-Dawley pups. At 24 hours after treatment with 2EH at 166.4 mg/kg, the number of Sertoli cells in the testicular sections was not diminished. 2EH does not alter the morphology of Sertoli cells and gonocytes.[124]

It was investigated whether 2EH is responsible for testicular damage. No testicular damage was observed in young rats orally administered with 2EH at 351 mg/kg/day for 5 days.[125] Additionally, administration of 2EH at 130 mg/kg/day for 14 days resulted in no testicular atrophy.[113]

In another study, 2EH were orally administered at 0, 50, 200, and 750 mg/kg to B6C3F1 mice 5 times a week for 18 months. The relative testicular weight was slightly increased in the groups treated with over 50 mg/kg/day 2EH. Similarly, 2EH was orally administered at 0, 50, 150, and 500 mg/kg five times a week to Fisher 344 rats for 24 months. 2EH induces a dose-dependent increase in testis weight.[21]

Mixed cultures of Sertoli and germ cells were prepared from the testes of 27- to 30-day-old Sprague-Dawley rats and the testicular toxicity was examined. The addition of 2EH at 2×10^{-4} M to the culture medium did not cause an increase in the rate of germ-cell detachment, compared with non-treated condition.[126]

Sertoli cells, which produce lactate and pyruvate are thought to be the initial target of testicular atrophy.[127] The effect of 2EH on lactate and pyruvate production was studied, but their production was unaffected by 2EH at 200 μmol/L.[128]

The antiandrogenic potential of 2EH in vitro with a mouse Leydig tumor cell line, MA-10 cells, was evaluated. 2EH did not have significant effects on cell viability and steroidogenesis.[129]

9 | MUTAGENICITY, CARCINOGENICITY, AND GENOTOXICITY

Doses of 16.7, 58.3, and 175 mg/kg/day to male Fischer 344 rats were administered by gavage for 5 consecutive days. 2EH did not induce detectable chromosomal aberrations.[130] Oral gavage doses of 2EH were administered 5 times a week to B6C3F1 mice at up to 750 mg/kg for 18 months and Fischer 344 rats at up to 500 mg/kg for 24 months. 2EH was not oncogenic in rats, but there were weak trends of adverse hepatocellular carcinoma incidence in mice at higher doses.[21]

There are several in vitro bacterial studies. Some group reported that 2EH was found to be mutagenic[131] and cause DNA damage.[132] However, other groups reported that 2EH was found to be non-mutagenic in the Ames test and Rec assay.[133-138]

Using a modified Ames *Salmonella*/microsome assay to determine mutagenicity, urine was pooled from male Sprague-Dawley rats dosed daily for 15 days with 1000 mg/kg of 2EH. No mutagenic substances were excreted in the urine.[139] 2EH also exhibited no chromosome damage[140] or mutagenic activity.[136]

In a carcinogenesis bioassay of DEHP and related compounds, it was reported that 2EH was not bound to hepatic DNA of Fischer 344 rats 24 hours following oral gavage administration.[141] In vitro promoting activity of DEHP and its hydrolysis product, 2EH, were studied using promotable

TABLE 5 Summary of the in vitro studies

Experimental conditions	Effects	Reference
The mitochondrial fraction of rat liver was treated with 1% 2EH	Low inhibitory effect on the state 3 respiration	143
Adult rat hepatocytes were cultured for 48 h in the presence of 0.2 and 1 mmol/L 2EH	Increased numbers of peroxisomes Increased activities of carnitine acetyltransferase and 7-ethoxycoumarin *O*-deethylase (at 1 mmol/L)	144, 145
Primary rat hepatocytes were cultured with 0-0.5 mmol/L 2EH for 72 h	No effect on CN^--insensitive palmitoyl-CoA oxidation	146
Cells of mice, rats, guinea pigs, and marmosets were cultured with 0.5 mmol/L 2EH for 72 h	Increased cyanide-insensitive fatty acyl CoA oxidase activity in mice and rats	147
Rat Kupffer cells were cultured with 1.25-3 mmol/L 2EH for 3 d	Increased intracellular calcium level at 3 mmol/L	148
Rat Kupffer cells were treated with 0.9 mmol/L 2EH	No effect on superoxide production	149
The cytosol of mouse and rat liver was treated with 15 mmol/L 2EH	Cytosolic GST was three times more potent in the mice than in the rats	150
Mouse liver was incubated with 0.25-1.00 mmol/L 2EH	Significant inhibition of ADH activity but no appreciable effect on ALDH activity	151
Rat liver was incubated with 2.5-15.0 mmol/L 2EH	Significant inhibition of the activities of aminopyrine N-demethylase and aniline hydroxylase	152
Mice spleen cells were incubated with 10^{-8}-10^{-3} mol/L 2EH for 24 h	IL-2 was induced in CD4 cells, but not in CD8 cells	153
Mice trigeminal ganglia neurons cells were incubated with 1-10 mmol/L 2EH	Activation expressed TRPA1 in a concentration-dependent manner	154,155
Perfused rat liver was incubated with 0.1-3 mmol/L 2EH	Extensive cell damage due to lactose dehydrogenase leakage	156
Perfused rat liver was incubated with 200 μmol/L 2EH	The rate of ketone body production was decreased to about 60%	117
Mitochondria isolated from perfused rat livers were treated with 70 μmol/L and 3 mmol/L 2EH	Inhibition of the oxygen uptake in the periportal regions, but not in the centrilobular regions	157, 158, 159

mouse epidermis-derived JB6 cells, which revealed that 2EH did not promote the anchorage of JB6 cells.[142]

10 | STUDY ON MODE OF ACTION OF 2EH

The in vitro effects of 2EH are summarized in Table 5. The administration of 2EH at a concentration of 1% to mitochondrial fractions from the liver of male Wistar rats exhibited insignificant inhibitory effect on State 3 respiration.[143]

Adult rat hepatocytes cultured for 48 hours in the presence of 0.2 mmol/L 2EH contained more number of peroxisomes than controls. The activity of carnitine acetyltransferase (a mixed peroxisomal/mitochondrial marker) and 7-ethoxycoumarin *O*-deethylase (microsomal marker) increased ninefold and twofold, respectively, by the presence of 1 mmol/L 2EH.[144,145]

The effect on peroxisomal enzyme activity in primary rat hepatocyte was determined after incubation with 2EH at 0-0.50 mmol/L for 72 hours. 2EH at these concentrations had no effect on the oxidation of the peroxisomal marker, cyanide-insensitive palmitoyl-CoA. Therefore, it was inferred that 2EH had no effect on peroxisomal β-oxidation.[146]

One study examined the possibility of species differences in response to 2EH. Hepatocytes were isolated from male mice, rats, guinea pigs, and marmosets, and incubated with 2EH. Although 2EH increased the activity of cyanide-insensitive fatty acyl CoA oxidase in mice and rats, did not increase in guinea pig and marmoset.[147]

Kupffer cells were isolated and incubated with 2EH, but no effect of 2EH on intracellular calcium and superoxide production.[148,149]

The inhibitory effect of 2EH on mouse and rat liver cytosolic GST activities was monitored in vitro. The study revealed that inhibition of GST by 2EH in mice was three times more potent than in rats.[150]

The activities of ADH and ALDH in mouse liver after 0.25, 0.50, and 1.00 mmol/L 2EH treatments were examined. The in vitro study revealed a significant inhibition of ADH activity by 2EH at concentrations of 0.50 and 1.00 mmol/L, but no appreciable effect on the activity of ALDH.[151]

2-Ethyl-1-hexanol at concentrations between 2.5 and 15.0 mmol/L significantly inhibited the activity of aminopyrine *N*-demethylase and aniline hydroxylase of rat liver.[152]

To investigate the effects of 2EH on immune responses, spleen cells from female BALB/c mice were incubated with 2EH. The activities of interleukin (IL)-6 and immunoglobulin were not induced by 2EH. IL-2 was induced by 2EH in CD4 cells, but not in CD8 cells. 2EH induced activation of CD4 cells, which was accompanied by the activation of transcription factors, suggesting that 2EH functions as a modulator of immune response.[153]

The effects of 2EH on heterologously expressed transient receptor potential (TRP) ion channels that cause sensory irritations in primary cell cultures of mice trigeminal ganglia neurons were investigated. 2EH activates heterologously expressed TRPA1 in a concentration-dependent manner (1-10 mmol/L). In Ca^{2+} imaging, 2EH acted as an agonist of multiple channels (TRPA1, TRPV1, GPCRs) which activate the trigeminal neurons.[154,155]

Although 2EH causes toxicity exclusively to periportal regions of the perfused liver, the toxicity is dependent on oxygen tension in isolated sublobular regions of the liver lobule. It is therefore unlikely for the selective injury to periportal regions in studies with perfused liver to be caused by drug delivery.[156] It was reported that 2EH inhibits β-oxidation of fatty acids in mitochondria, but not in peroxisomes.[117]

A second group also assessed 2EH toxicity in the liver. Livers from starved female Sprague-Dawley rats were perfused with 2EH (at 3 mmol/L) dissolved in Krebs-Henseleit buffer (pH 7.4, 37°C) saturated with 95% O_2, 5% CO_2. Following infusion of 2EH, O_2 uptake and ketone body formation were diminished by 50% and 80%, respectively. Furthermore, cell damage, as assessed by the appearance of LDH in the effluent perfusate, was apparent. Only O_2-rich upstream regions of the liver lobule were damaged. This toxicity is dependent on oxygen tension in isolated sublobular regions of the liver lobule. Peroxisome proliferators accumulate in the liver due to their lipophilicity. They inhibit actively respiratory mitochondria in the periportal region of the hepatic lobule and cause partially toxicity.[157-159]

11 | CONCLUDING REMARKS

In this review, we focused on the toxicity of 2EH from the viewpoint of an indoor air pollutant.

2EH is metabolized to 2-ethyl-1-hexanal, and then to 2EHA, after which it is rapidly excreted from the body. However, drug-metabolizing enzyme activity reportedly varies greatly among individuals.[28] Thus, long-term exposure to 2EH, especially in populations with low metabolic activities, may cause health effects even below the minimum concentration that causes toxic effects.

In both Japan and Northern Europe, 2EH was detected in buildings where patients complained of SBS symptoms.[7,54] 2EH has been reported to induce mucosal irritation and effects on the central nervous system. Thus, 2EH is considered among the causative agents of SBS symptoms.

Reports on the effects in animals of inhalation exposure to 2EH are limited. In particular, there is no report on the liver effects of its inhalation exposure. Orally ingested 2EH

increases the number of peroxisomes. Peroxisome proliferators activate peroxisome proliferator-activated receptor α (PPARα) and affect lipid metabolism, inflammation, glucose homeostasis, cell proliferation, and apoptosis.[160] Because 2EHA, a metabolite of 2EH, acts as a PPARα agonist,[161] it may be responsible for the effects observed upon 2EH oral administration on the liver.

In most buildings where the 2EH indoor air concentrations are high, plasticizer-containing flooring materials have a direct contact with concrete. There are multiple sources of 2EH in rooms, that is, primary emission from PVC products and/or building materials, and secondary emission resulting from chemically induced hydrolysis and/or microbial decomposition of plasticizers and/or adhesives.

It was reported that 2-butanol is generated through the hydrolysis of several acrylic adhesives.[65] *n*-Butanol is emitted from the floor,[66] produced from di-*n*-butyl phthalate,[162] and 2-butanol from isobutyl phthalate.[162] As a measure against VOCs emissions like that of 2EH, it is very important to use a flooring or other building material that does not emit VOCs even from the hydrolysis reaction, or to confirm that the moisture content in the concrete is sufficiently lowered before flooring the room.

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CONFLICT OF INTEREST

None declared.

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