



Persistent, bioaccumulative, and toxic properties of liquid crystal monomers and their detection in indoor residential dust

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Liquid crystal monomers (LCMs) are used widely in liquid crystal displays (LCDs), which are dramatically changing the world due to the provision of convenient communication. However, there are essentially no published reports on the fate and/or effects of LCMs in the environment. Of 362 currently produced LCMs, 87 were identified as persistent and bioaccumulative (P&B) chemicals, which indicated that these chemicals would exhibit resistance to degradation and exhibit mobility after entering the environment. Following exposure to mixtures of LCM collected from 6 LCD devices, significant modulation of 5 genes, *CYP1A4*, *PDK4*, *FGF19*, *LBFBP*, and *THRSP*, was observed *in vitro*. Modulation of expressions of mRNAs coding for these genes has frequently been reported for toxic (T) persistent organic pollutants (POPs). In LCM mixtures, 33 individual LCMs were identified by use of mass spectrometry and screened for in 53 samples of dust from indoor environments. LCMs were detectable in 47% of analyzed samples, and 17 of the 33 LCMs were detectable in at least 1 sample of dust. Based on chemical properties, including P&B&T of LCMs and their ubiquitous detection in dust samples, the initial screening information suggests a need for studies to determine status and trends in concentrations of LCMs in various environmental matrices as well as tissues of humans and wildlife. There is also a need for more comprehensive *in vivo* studies to determine toxic effects and potencies of LCMs during chronic, sublethal exposures.

liquid crystal displays (LCDs) | liquid crystal monomers (LCMs) | persistence (P) | bioaccumulation (B) | toxic (T)

The demand for liquid crystal displays (LCDs) has increased since the 1990s with rapid increases in the use of personal computers, digital cameras, digital televisions, mobile phones, and intelligent electronic products (1). Liquid crystal monomers (LCMs) have been widely used in LCDs, which rely on the optical properties of certain liquid crystalline substances in the presence or absence of an electric field. A consulting business reported that in 2018, the global shipment of LCD panels rose to 198 million m² (2). With an increasing number of LCD panels being put into production worldwide, the demand for LCM materials is rapidly increasing. Old LCD devices eventually become electronic waste (e-waste), which is typically discarded—at best in proper e-waste sites—and thus poses serious environmental concerns and challenges. However, environmental behavior, fate, and adverse effects of LCMs have not been reported, and even the specific physical–chemical properties of LCMs have not been very well studied.

LCMs represent a state of matter that flows similar to a liquid but consists of anisotropic compounds (3, 4). At typical ambient temperatures, properties of LCMs are intermediate between liquid and solid states (5). LCMs were first discovered by Reinitzer (6), and since then, thousands of LCMs, with various chemical structures, have been synthesized and commercialized.

Typical LCMs are considered to have the following properties: 1) most have aromatic nuclei that are polarizable, planar, and rigid; 2) the central group in the molecule usually contains a multiple bond along the long axis of the molecule or a system of conjugated double bonds that makes the molecule rigid and planar; and 3) the length of the molecule is generally greater than its diameter (7). Manufacturers can enhance performances of LCMs by changing the terminal functional group by introducing a side chain or replacing phenyl groups with a cyclohexyl ring (8). These chemical moieties can result in various structures for LCMs, which can exhibit differential persistence and bioaccumulation potentials (P&B) once they enter the environment.

To the best of our knowledge, current research and legislation/regulations on handling and disposal of e-waste focuses primarily on metals or metalloids, flame retardants, and ozone-depleting substances, but no regulations exist for LCM materials (9). Even though key materials in LCDs are mixed LCMs, there are essentially no published reports on occurrences or hazards posed by LCMs (10, 11). Information regarding structures of LCMs is normally kept confidential among manufacturers of LCs or LCDs. Thus, studies of effects of LCMs on biota are relatively rare (10). A large producer of LCMs once claimed that those used

Significance

Liquid crystal devices, such as smartphones, televisions, and tablet computers, have become integral tools of modern society; however, people do not know the environmental effects of liquid crystal monomers (LCMs). The present study conducted an extensive survey on industries producing LCMs and generated a list containing 362 current-produced LCMs. Eighty-seven out of 362 LCMs showed potential as P&B chemicals, indicating that these LCMs would exhibit resistance to degradation and high mobility after entering the environment. Beyond that, we observed that exposure to LCMs resulted in adverse effects during *in vitro* screening, by use of cell culture and toxicogenomic evaluation, that were similar to effects observed for other persistent organic pollutants, and that some LCMs were detectable in samples of indoor dust.

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commercially were not harmful to fish during short-term exposures to relatively high concentrations, relative to what would be expected to occur in surface waters (10). However, the absence of acute effects does not necessarily mean that LCMs have no persistent, bioaccumulative, and/or chronic toxic (T) properties (10, 12).

In silico screening of substances to determine if they are P&B typically relies on quantitative structure property relationships (QSPRs) to predict P&B properties, and various jurisdictions have different criteria set as thresholds to determine if a substance is considered to be P and/or B (13). In previous studies, investigators have successfully identified P and B organic chemicals (14, 15) and pharmaceuticals (16, 17) in commerce. Estimation Programs Interface (EPI) Suite software has effectively estimated physical chemical parameter values for a range of chemicals classes (18). By use of these techniques, in 2018, our research group published a viewpoint based on a list covering more than 300 LCMs, and we challenged environmental chemists to pay attention to potential P&B LCMs (11). We also noted that identification and quantification of LCMs in environmental media has not been reported, and emissions and fates of LCMs remained largely unknown.

Current releases or concentrations of LCMs in various compartments used to produce commercial LCDs are not known, although potential adverse effects on wildlife and the general environment have been suggested (19, 20). In this study, the primary objectives were to 1) provide a list of the 362 LCMs previously reported in our viewpoint article, where P&B properties were discussed; 2) examine mRNA expression of 43 genes following exposure of chicken embryonic hepatocytes (CEHs) to 6 LCM mixtures from largely produced and used LCD devices; 3) identify chemical structures of LCMs in these collected mixtures; and 4) investigate occurrences of LCMs identified in LCD devices in indoor dust.

Results and Discussion

The workflow of this entire study is summarized in Fig. 1, which includes calculation of P&B properties of 362 LCMs, toxicity assessment of LCM mixtures from LCD devices, identification of chemical structures in LCM mixtures, and occurrence of LCMs in dust samples.

Current Status of Use and Production of LCD and LCM around the World. At the core of the global, modern display industry, LCD panels are almost exclusively produced in 3 Asian countries: China, Japan, and South Korea. At present, China is the world's largest producer of the latest generation LCD panels. The distribution of manufacturers of LCMs and LCDs around the world

and in China are illustrated in *SI Appendix, Figs. S2 and S3*, respectively.

In 2017, global demand for thin film transistor-LC (TFT-LC) materials was 960 tons, of which the demand in mainland China was 320 metric tons (21). With an increasing number of LCD panel production lines in mainland China, the demand for TFT-LC materials is rapidly increasing. The top 3 positions for production of high-performance TFT-LC materials were held by 3 large firms in the global LC materials market (21), while the upstream materials for LCDs, such as monomers and intermediate products, were mainly produced in China.

During production of LCD devices, LCMs are simply filled into the space between polarizers and are not chemically bonded to any base material. This means that throughout the life cycle of LCM-containing devices, they exhibit greater potentials to be released into the environment. That is, they can be released during production; through wastewater; or during active use, disposal, or recycling. For many years, huge amounts of globally produced e-waste have been dismantled, disposed, and introduced into environments (5). It is likely that during these relatively low-tech recycling practices of recovering metal or indium from LCD devices, LCMs could enter local environments (19).

Assessment of P&B Properties for 362 LCMs. Since information on compositions of mixed LCMs is normally confidential business information, and relative proportions of LCMs in these devices are constantly updated, it is difficult to study the chemical properties of LCMs. Ten industries that produce LCMs were presently surveyed, and a list containing 362 commercial LCMs was developed. These 362 current-use LCMs were screened by use of the QSPRs program and expert judgment of persistence and bioaccumulation (13, 14, 16).

All 362 LCMs were individually evaluated to identify if they were P or B or both by use of the US Environmental Protection Agency's (US EPA) EPI Suite software (18) (Table 1), along with details of the regulation, guidance document, or publication that provided the screening criteria. For LCMs that exhibited $\log K_{ow}$ values greater than 5 or bioconcentration factor (BCF) values greater than 1,000, the chemical was considered to be B. The US EPA established that BCF values between 100 and 1,000 indicate a moderate level of concern based on potential B of chemicals under the proposed rule for P&B chemicals (22). The BCF cutoff value of 1,000 for a high level of concern for bioaccumulation potential has been used over the years; in the context of the Stockholm Convention, criteria were listed in Annex D to identify whether a chemical is considered bioaccumulative, with the first criterion being a $\log K_{ow} > 5$ (23). LCM chemicals with high $\log K_{ow}$ values were considered to be

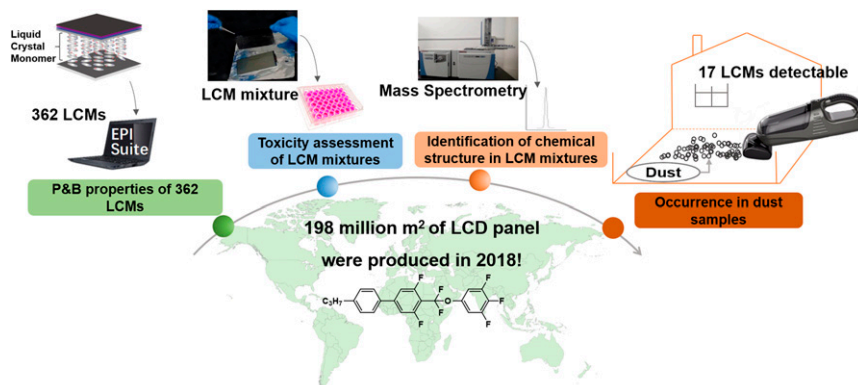


Fig. 1. Workflow of the present study, which includes calculation of P&B properties of 362 LCMs (Fig. 2), toxicity assessment of LCM mixtures from LCD devices (Fig. 3), identification of chemical structure in LCM mixtures (Fig. 4), and detection of LCMs in dust samples (Fig. 5).

Table 1. Persistence and bioaccumulation characteristics of 362 LCMs

Characteristics	Number	Percent	Notes
Log K_{ow}^* > 5	340	93.9	Indicates tendency to adsorb to sediments and to bioaccumulate.
BCF > 1,000	202	55.8	BCF is an estimate of bioaccumulation potential.
BCF > 5,000	68	18.8	
AO $t_{1/2}^\dagger$ > 2 d	1	0.3	AO $t_{1/2}$ indicates stability to atmospheric oxidation.
Log K_{aw}^\ddagger > -5 and log $K_{aw} < -1$	205	56.6	K_{aw} describes air-water partitioning. Compounds with log K_{aw} > -5 and < -1 have long-range transport potential.
$t_{1/2, w}^\S \geq 60$ d	171	47.2	/
Combined Log K_{ow} > 5, Log K_{aw} > -5 and < -1, and $t_{1/2, w} \geq 60$ d	87	24.0	/
Combined Log K_{ow} > 5, Log K_{aw} > -5 and < -1, BCF > 5,000 and $t_{1/2, w} \geq 180$ d	10	2.8	The number of substances with all 3 characteristics combined is much smaller.

*Log K_{ow} , octanol-water partition coefficient.

† AO $t_{1/2}$, atmospheric oxidation half-life.

‡ Log K_{aw} , atmosphere-water partition coefficient.

§ $t_{1/2, w}$, biodegradation half-life in water.

potentially B, even though many QSPRs suggest that BCF decreased with log K_{ow} > 6 (13). Generally, a chemical compound is considered potentially P if the values from BIOWIN¹ or BIOWIN⁵ models are less than 0.5 (not readily biodegradable) (24). In accordance with the rules of thumb (13) (e.g., persistent being more halogenated, more branched, and nitroaromatic and biodegradable being straight-chain aliphatic compounds, esters, acids, and hydroxyl functional groups), if chemicals had some of these functional groups, they were considered to be potential P chemicals. Combined with biodegradation half-life values in water ($t_{1/2} \geq 60$ d) and aerobic biodegradable values (BIOWIN¹ or BIOWIN⁵), probable P&B chemicals were selected. Of these P&B chemicals, LCMs were considered to be very persistent and very bioaccumulative (vPvB) if BCF values were greater than 5,000 and half-lives in water were greater than 180 d (Fig. 2).

Based on these criteria, of the 362 chemicals, a significant proportion were predicted to be B; 340 were estimated to have log $K_{ow} \geq 5$, and 202 were estimated to have BCF of >1,000 (SI Appendix, Table S1) (13). A total of 205 LCMs were rated as potentially susceptible to long-range atmospheric transport (log $K_{aw} \geq -5$ and ≤ -1). Chemicals were considered to be potentially P if degradation half-lives in water exceeded 60 d (16). By using the following 3 properties—1) log $K_{ow} \geq 5$, 2) log $K_{aw} \geq -5$ and ≤ -1 , and 3) $t_{1/2} \geq 60$ d—87 LCMs were classified as potentially P&B (Fig. 2). All LCMs that were classified as P&B were fluorinated, which is consistent with generally greater P&B characteristics of halogenated compounds (13).

Of the 87 LCMs classified as P&B, a C≡C triple bond was apparent in 16.4%, while 29.9% included an ester group, and 43.7% were biphenyl/triphenyl compounds. To reduce the list of 87 to a more manageable number, 10 priority substances were selected for further evaluation that satisfied the following properties: log $K_{ow} \geq 5$, BCF > 5,000, BIOWIN¹ < 0.5, and $t_{1/2, w} \geq 180$ d (SI Appendix, Table S2).

All LCMs listed in SI Appendix, Table S2, are fluorinated with various central and terminal groups. The first and second chemicals, 4'-ethyl-2',3,4,5-tetrafluoro-1,1':4',1''-terphenyl (Chemical Abstracts Service Registry Number [CASRN] 326894-55-7) and 2',3,4,5-tetrafluoro-4'-propyl-1,1':4',1''-terphenyl (CASRN 205806-87-7), are triphenyl homologs with similar estimated properties. Both have an estimated log K_{ow} > 7, log K_{aw} between -5 and -1, and $t_{1/2, w} = 180$ d, which indicates that these chemicals are predicted to be potentially vP and vB. The 4 fluorine atoms have an electron-withdrawing effect and at the terminus of chemicals can easily show the formation of an accumulative effect; the electron

cloud migration is large, thus showing a large dielectric anisotropy. Therefore, polyfluorinated triphenyls are used in high-performance TFT-LC materials as medium polar substances to enhance electrical conductivity. However, toxic potencies estimated by ECOSAR indicated that these chemicals might exhibit acute effects, and estimated BIOWIN¹ and BIOWIN⁵ of approximately -0.26 and -0.18 showed that these chemicals are not readily biodegradable.

The third and fourth chemicals, 1-ethoxy-2,3-difluoro-4-(4-ethylcyclohexyl) benzene (CASRN 415915-41-2) and 1-ethoxy-2,3-difluoro-4-(4-propylcyclohexyl) benzene (CASRN 174350-05-1), are phenyl cyclohexyl LCs, which are ideal display materials because they have high chemical and photochemical stability. Both fluorine atoms and the oxygen atom in the ethoxyl group form a p- π conjugated structure with the phenyl ring, increasing electron cloud density and dipole moment. In addition, the transstructure of cyclohexyl can develop close packing in the molecular

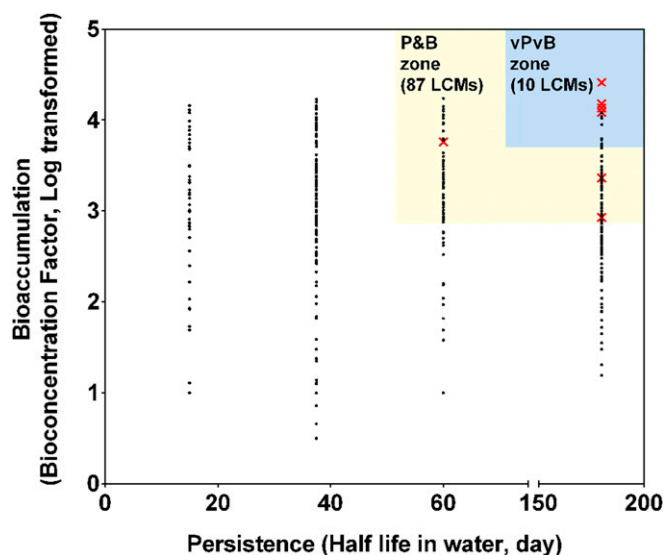


Fig. 2. Distribution persistence (half-life in water) and bioaccumulation (BCF) of 362 LCMs compared to typical POPs, i.e., PBDEs (BDE-47, BDE-99, BDE-154, and BDE-183), hexabromocyclododecane (HBCDD), and PCBs (CB-157 and CB-189). The black dots represent individual LCMs, and the red crosses represent the POPs.

structure, thus exhibiting a greater clearing point than biphenyl LCs. Both the third and fourth chemicals have estimated BCFs > 10,000 and log K_{ow} values of ~7, which indicates potentially large B. When all of the estimates from BIOWIN were considered, they were both suggested to be P. Both were predicted to have an $AOI_{1/2}$ value of < 1 d, reflecting the predicted instability of the chemicals toward atmospheric oxidation by OH-radical reactions.

Currently, fates and effects of LCMs in the environment are rarely studied. Thermotropic LCs (4-n-pentyl-4'-cyanobiphenyl, 4-cyano-4'-n-heptyl-biphenyl, 4-cyano-4'-n-oxyoctyl-biphenyl and 4-cyano-4'-n-pentyl-terphenyl) were toxic to fungal spores (12). All these LCs were included in our database, with the chemical 4-n-pentyl-4'-cyanobiphenyl predicted to have a log K_{ow} value of ~5.8, log K_{aw} of -3.25, BCF > 3,000, and $AOI_{1/2}$ > 1 d, which was indicative of potential for bioaccumulation and long-range atmospheric transport. Due to the absence of the central group, biphenyl and triphenyl chemicals are more stable than other LCMs and, thus, exhibit lesser susceptibility to microbial degradation and enhanced possibility for persistence and bioaccumulation (SI Appendix, Table S1).

Electrical and electronic equipment is widely used in the world, but there are no standards and few relevant research reports on recycling of LCMs in e-waste (10, 12). Thus, potential environmental effects of LCMs are poorly measured and difficult to predict. This study has yielded some probable P&B LC substances that should be considered for further study and monitoring of concentrations in various environmental matrices.

Investigation of Toxicity of Mixtures of LCM from Current-Use LCD Devices. PCR array technology is a reliable approach to investigate adverse effects of environmental contaminants (25, 26). To investigate whether exposure to mixtures of LCM from $n = 6$ current-use LCD devices resulted in changes in expressions of

selected mRNAs in CEHs, an avian ToxCip, which measures the expression of mRNAs coding for 43 genes from 9 biological pathways including bile acids/cholesterol regulation, cell cycle, DNA repair, glucose metabolism, immune response, oxidative stress, the thyroid hormone pathway, lipid homeostasis, and xenobiotic metabolism, was used (SI Appendix, Table S3). Five genes, *CYP1A4*, *FGF19*, *LBFABP*, *PDK4*, and *THRSP*, were significantly dysregulated following exposure to 2 units per mL LCM mixtures (note that 1 unit represents the amount of LCM mixture that was dissolved from 1 in. of LCD devices) (Fig. 3A). These 5 gene targets were involved in xenobiotic metabolism, bile acids/cholesterol regulation, lipid homeostasis, glucose metabolism, and the thyroid hormone pathway, respectively.

Expression of *CYP1A4* is modulated by the aryl hydrocarbon receptor (AhR), which is the main receptor that interacts with, and binds to, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and other dioxin-like chemicals (27). Here we observed significant up-regulation of *CYP1A4* in CEHs following exposure to LCM mixtures 2, 3, 4, and 6 (Fig. 3B), which might indicate that LCM mixtures could act like dioxin-like compounds to induce hepatic cytochrome P450-dependent arachidonic acid epoxygenation. *FGF19*, which is associated with bile acids/cholesterol regulation, was up-regulated in CEH following exposure to LCM mixtures 2, 3, 4, and 6 (Fig. 3B). *FGF19* plays an important role in digestion and absorption of lipids from the small intestine and is involved with regulation of bile acid biosynthesis, gallbladder filling, and glucose and metabolism of lipids (28). *LBFABP* is associated with lipid homeostasis and was significantly up-regulated in CEH following exposure to mixtures 2, 3, 4, and 6. *LBFABP* encodes the liver basic fatty acid binding protein, which is involved in binding, transport, and metabolism of long-chain fatty acids and lipids such as cholesterol and bile acids (29). *PDK4*, which is associated with metabolism of glucose, was significantly ($P < 0.05$)

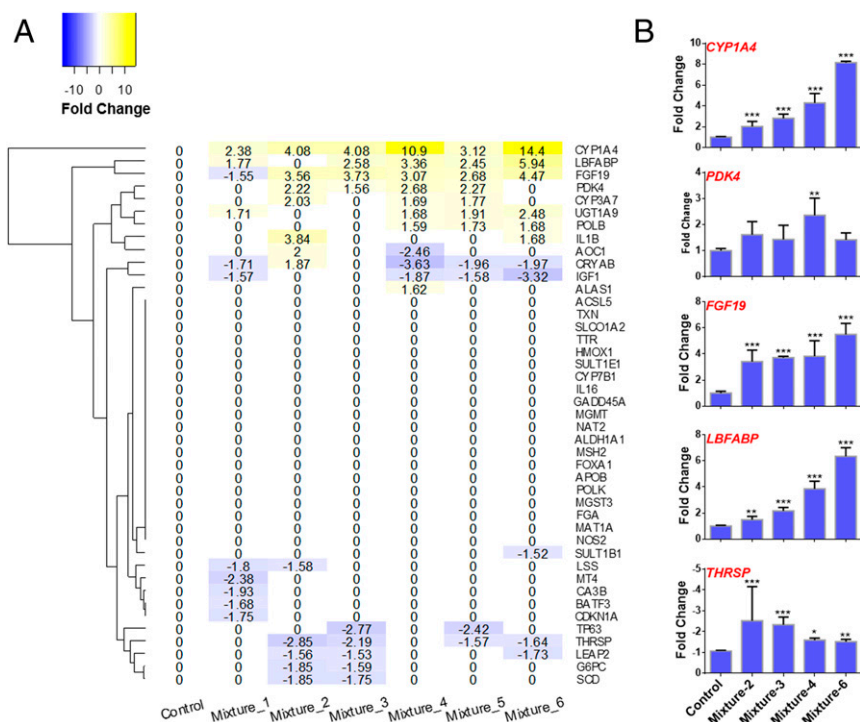


Fig. 3. Alteration of mRNA expression in CEHs exposed to LCM mixtures of 6 current-use LCD devices. (A) Transcriptional profiles of 43 genes on the Avian ToxCip PCR array following exposure to 2 units/mL mixtures of LCM (note that 1 unit represents the amount of LCM mixture that was dissolved from 1 in. of LCD devices). (B) Confirmation of alteration of mRNA expression of 5 target genes (*CYP1A4*, *PDK4*, *FGF19*, *LBFABP*, and *THRSP*; error bars for each point are the SD of 3 replicates) by use of real-time PCR (pairwise P values were determined for each treatment compared to the DMSO vehicle control group; * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$).

up-regulated following exposure to LCM mixture 4. *PDK4* is associated with conversion of glucose to acetyl-CoA, which is associated with energy generation and maintaining the balance between metabolisms of carbohydrates and lipids (30). *PDK4* was also dysregulated in CEH following exposure to a toxic organophosphate ester (OPE) contaminant, TDCIPP (31). *THRSP*, which is associated with the thyroid hormone pathway, was down-regulated following exposure to LCM mixtures 2, 3, 4, and 6. The thyroid hormone pathway plays an important role in normal central nervous system development in birds, among many other critical roles (32). Similar alterations of *THRSP* were also previously reported for organic flame retardants, including *PBDEs*, *TPHP*, and *EHDPP*, which were identified as potent competitors for thyroxine binding to TTR (33, 34).

Among 43 genes associated with 9 biological pathways represented on the ToxCip, multiple genes were responsive to mixtures that contained LCMs and provided some initial insight regarding mechanisms of toxicity of LCMs. These genes/pathways were previously reported to be responsive following exposure to other halogenated environmental contaminants, i.e., dioxin-like compounds (*CYPIA4*) (33, 34) and flame retardants (*FGF19*, *LBFABP*, *PDK4*, and *THRSP*) (26).

Identification of Chemical Structures of LCMs in Current-Use LCD Devices. As key materials in electronic displays, individual LCMs could not satisfy the complex and diverse requirements of displays; thus, mixtures of LCMs are carefully balanced in LCDs. Here specific chemical structures of LCMs were further identified in 6 LCM mixtures that were used for toxicity assessment in *Investigation of Toxicity of Mixtures of LCM from Current-Use LCD Devices*.

Eluates containing a mixture of LCMs were analyzed in full-scan mode by gas chromatography-mass spectrometry (GC-MS). Using the mass spectrogram, the preliminary chemical structures

could be predicted and matched with peaks. Based on the predicted structures, 10 pure chemicals were purchased and analyzed by GC-MS. Based on retention times and fragment ions, 10 LCMs were identified, and LC-Q Exactive MS was used to verify exact masses from which molecular formulae could be derived by comparing the detected mass with the exact mass.

All 33 LCMs in the mixtures were identified and structures written, based on fundamentals of mass spectrometry similar to those suggested previously (Fig. 4 and *SI Appendix, Fig. S5*) (35–39). Mass spectra of LCMs 5, 9, 13, 16, 31, and 33 have been published previously (35, 40). In our study, the 33 LCMs could be placed into 3 major categories, and mass spectra of those 3 classes of LC chemicals (*SI Appendix, Tables S4–S6*) and mass spectra and possible fragmentation pathways are shown in *SI Appendix, Fig. S4*.

All 33 identified LCMs were on our list of LCMs (*SI Appendix, Table S1*), and properties of the 33 LCs, identified by electron impact ionization (EI) mass spectra, are in *SI Appendix, Table S7*. All 33 LCMs have estimated $\log K_{ow} > 5$, and more than 50% have $BCF > 1,000$, which indicates that after entering into the environment, most of the identified LCMs in phones have potential for bioaccumulation. Of the 33 identified LCMs, 25 were predicted to have $t_{1/2,w} \geq 60$ d, 28 had an estimated $BIOWIN^1 < 0.5$, and all 33 LCMs had an estimated $BIOWIN^5 < 0.5$, which indicates significant persistence of LCMs currently used in LCDs. Fourteen LCMs had predicted $\log K_{aw} \geq -5$ and ≤ -1 , which indicated potential for long-range atmospheric transport. Based on these 3 properties ($\log K_{ow} \geq 5$, $BCF > 1,000$, and biodegradation $t_{1/2,w} \geq 60$ d), 9 LCMs were classified as potential P&B.

Most of the LCMs in LCDs of frequently used smartphones were predicted to exhibit bioaccumulation or persistence in the environment (*SI Appendix, Table S7*). Of the 33 LCMs, 26 were fluorinated, which indicates generally longer persistence and bioaccumulative potential of those halogenated LCMs to cause

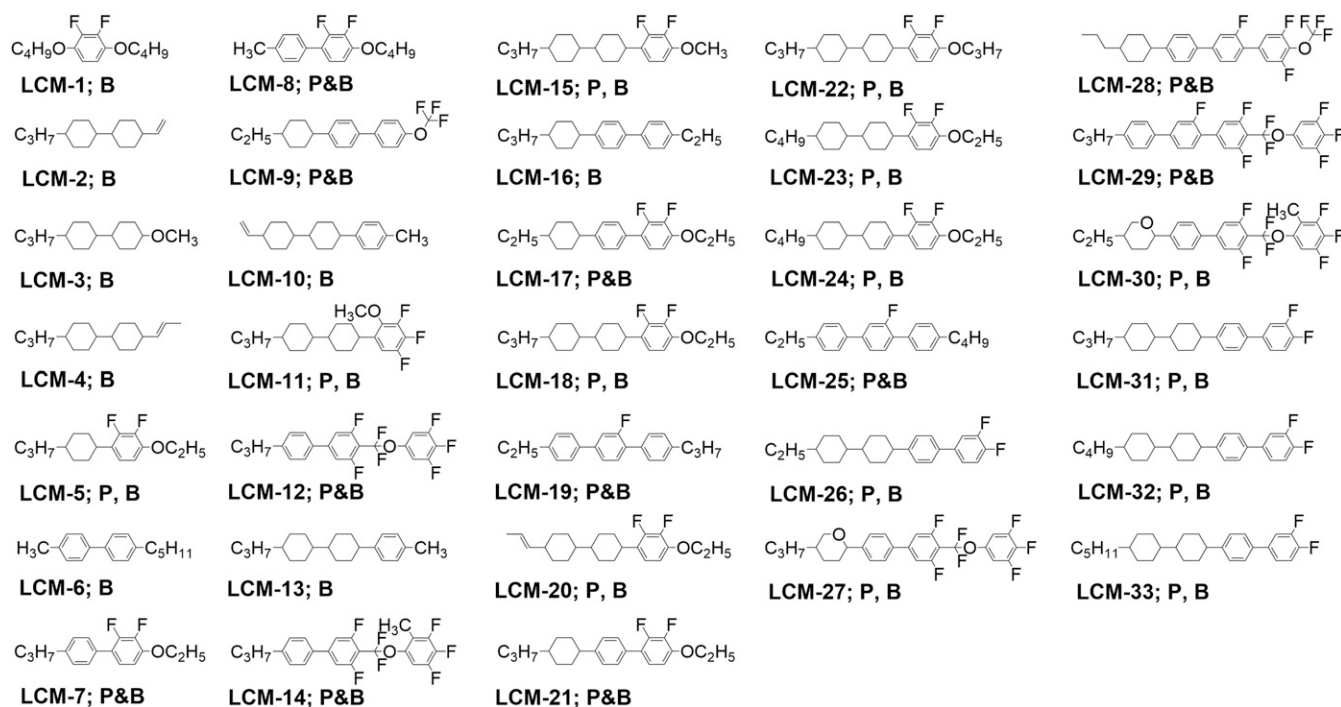


Fig. 4. Chemical structures and P&B properties of 33 LCMs that were identified in the LCM mixtures of 6 commercial LCD devices. In this figure, P refers to persistence (a chemical was considered P if the value for the $BIOWIN^1$ or $BIOWIN^5$ models was less than 0.5 or the chemical molecule had certain functional groups [e.g., persistent: highly halogenated, highly branched]). B refers to bioaccumulation, and a chemical was considered to be B if $\log K_{ow} > 5$ or BCF values were greater than 1,000. P&B refers to persistence and bioaccumulation (i.e., those chemicals with $\log K_{ow}$ and $t_{1/2,w}$ values greater than 5 and 60 d, respectively, and $\log K_{aw}$ values between -5 and -1). Specific information (i.e., full name and chemical properties) for all 33 LCMs can be found in *SI Appendix, Table S7*.

adverse environmental effects if they enter the environment. The 1-(4-propylcyclohexyl)-4-vinylcyclohexane (LCM-2, CASRN 116020-44-1), which was detected in all 6 LCDs of the commercial cellphones studied, has an estimated log K_{ow} and BCF of ~ 8 and 4,000 respectively, which is indicative of potential for bioaccumulation. The 1-ethoxy-2,3-difluoro-4-(4-propylphenyl) benzene (LCM-7, CASRN 157248-24-3), 4-ethoxy-4'-(4-ethylcyclohexyl)-2,3-difluorobiphenyl (LCM-17, CASRN 323178-01-4), 1-ethoxy-2,3-difluoro-4-(4-(4-propylcyclohexyl) cyclohexyl) benzene (LCM-18, CASRN 123560-48-5), 4-ethoxy-2,3-difluoro-4'-(4-propylcyclohexyl) biphenyl (LCM-21, CASRN 189750-98-9), and 1-(4-(4-butylcyclohexyl) cyclohexyl)-4-ethoxy-2,3-difluorobenzene (LCM-23, CASRN 473257-15-7), which were detected in 4 of 6 commercial LCDs, were all predicted to be P&B.

We suggest that further studies should be conducted on these 33 LCMs that are currently being used in commercial LCDs to determine their status and trends in concentrations in various environmental matrices as well as tissues of humans and wildlife.

Screening of 33 Identified LCMs in Indoor Dust Samples. To our knowledge, no quantitative analytical methods exist for LCMs in environmental matrices. In our study, preparation and extraction of samples for the determination of LCMs in dust were similar to those for extracting brominated flame retardants from sediments (41, 42). Because of its efficiency, reproducibility, minimization of solvent use, and minimal background interference, accelerated solvent extraction (ASE) was used to extract LCMs from dust (43). When samples were analyzed by GC-MS/MS, the relative abundance and retention times were used to initially identify the 33 target LCMs. Details of validation parameters and spike recoveries for determination of LCMs are provided in *SI Appendix, Table S8*. Seventeen LCMs, including LCM-2, LCM-3, LCM-5, LCM-6, LCM-7, LCM-10, LCM-12, LCM-13, LCM-15, LCM-17, LCM-18, LCM-20, LCM-21, LCM-22, LCM-23, LCM-28, and LCM-30, were detected in 47% of samples of indoor dust, whereas the others were not quantifiable in any of the analyzed samples (Fig. 5A and *SI Appendix, Table S9*). Among the 53 samples of dust, concentrations of Σ_{33} LCM ranged from 0.13 to 2,213 ng/g, dry mass (dm), and more than 80% of the total sum concentration of LCMs comprised LCM-15, LCM-18, LCM-20, and LCM-23. In the present study, concentrations of LCMs varied among sources of dust. For example, the mean Σ_{33} LCM concentration in dust from the laboratory building was 374 ng/g, dm, compared to dust from the canteen (3.64 ng/g, dm). The rank order (from lowest to highest) of mean concentrations of Σ_{33} LCM in dust from buildings was canteen < dormitory <

teaching building < hotel < electronic product maintenance center < residence < laboratory building.

Among the 17 LCMs detected in the 53 analyzed dust samples, LCM-5, LCM-7, LCM-12, LCM-15, LCM-17, LCM-18, LCM-20, LCM-21, LCM-22, LCM-23, LCM-28, and LCM-30 were fluorinated chemical compounds (*SI Appendix, Table S9*). This pattern of LCMs was generally comparable with predictions that fluorinated LCMs exhibited greater potential for P&B. Fluorinated LCMs, especially LCM-12, were detected in all 7 sampling spaces (Fig. 5A); however, there was no obvious trend that concentrations of fluorinated LCMs in the same area were greater than unfluorinated LCMs.

To study characteristics of LCMs relative to other contaminants in indoor dust, concentrations of OPEs, polybrominated diphenyl ethers (PBDEs), and novel brominated flame retardants (NBFRs) were also measured. Details of analysis methods used for OPEs, PBDEs, and NBFRs are described in *SI Appendix*. Compared to concentrations of conventional contaminants in the same indoor dust samples (Fig. 5B), concentrations of Σ_{33} LCM were less than those of Σ OPEs, Σ PBDEs, and Σ NBFRs. Unlike conventional flame retardants, applications of most LCMs are limited to electronic equipment, and large-scale use of LCMs has been relatively recent. This could help explain the lesser concentrations of LCMs compared to additive flame retardants in the dust samples (Fig. 5B).

Comparison with Typical Persistent Organic Pollutants and Significance.

Persistent organic pollutants (POPs) defined under the Stockholm Convention (44) and the list of carcinogens from the World Health Organization have informed elimination and/or production and use restriction for flame retardant additives such as 2,2',4,4'-tetrabromodiphenyl ether (BDE-47) (in 2009), 2,3,3',4,4',5'-hexachlorobiphenyl (CB-157) (in 2004), and hexabromocyclododecane (HBCDD) (in 2013). It has been confirmed that these flame-retardant additives are persistent in the environment and have a strong potential to bioaccumulate and biomagnify in organisms (45). These chemicals have potential for long-range environmental transport and have been detected in tissues of humans from many regions (46). There is evidence of potential toxic effects in aquatic organisms, including mammals (47, 48). Similar to PBDEs and polychlorinated biphenyls (PCBs), LC chemicals, which were predicted to have potential P and B based on our findings, are all halogenated. Due to the lack of experimental data regarding LCMs, we used estimated properties (degradation half-life in water, BCFs, and fish chronic toxicity values) to compare LCMs with PBDEs, HBCDD, and PCBs. In this study, we selected the 5 most frequently detected brominated flame retardants (BDE-47, BDE-99,

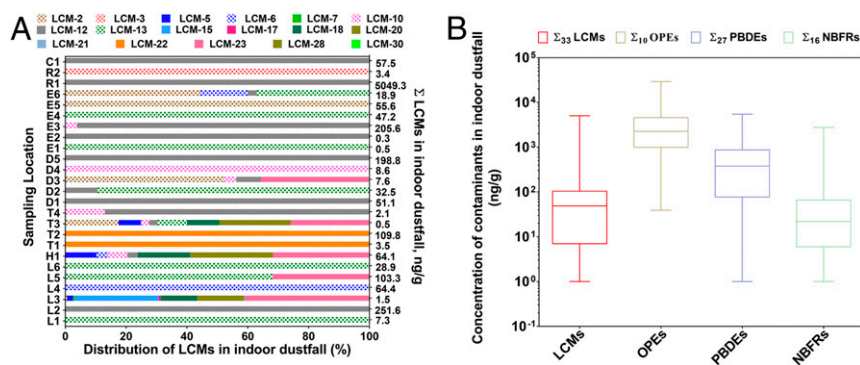


Fig. 5. Screening identified 33 LCMs in samples of indoor dust that were collected from 7 indoor spaces in Nanjing, China. (A) Distribution pattern of LCMs that had detectable concentrations ($n = 25$ samples) in indoor dust samples at different sampling spaces (C, R, E, D, T, H, and L represent the sampling spaces: canteen, residence, electronic product maintenance center, dormitory, teaching building, hotel, and laboratory building, respectively). (B) Box plot showing the total log-transformed concentrations (ng/g) of 33 LCMs compared to typically monitored environmental contaminants (i.e., Σ_{10} OPEs, Σ_{27} PBDEs, and Σ_{16} NBFRs) in $n = 53$ dust samples from $n = 7$ sampling spaces). The upper, middle, and lower lines in the box represent the 75th, 50th, and 25th centiles, respectively, whereas the lower and upper bars represent the minimum and maximum values, respectively.

BDE-154, BDE-183, and HBCDD) and 2 polychlorinated biphenyls (CB-157 and CB-189) in the environment to compare with the 362 LCMs (Fig. 2).

All selected PBDEs and PCBs have an estimated half-life in water ($t_{1/2,w}$) of 180 d and $2.0 \leq \log BCF \leq 4.5$ ($800 \leq BCF \leq 15,000$ L/kg, wet mass [wm]); HBCDD has an estimated half-life in water of 60 d and BCF of 5,759 L/kg, wm. LCMs were classified as P&B if the biodegradation half-life values in water exceeded 60 d and $BCF \geq 1,000$. Therefore, predicted properties for P&B LCMs are generally similar to those of PBDEs, HBCDD, and PCBs, indicating the potential for LCMs to persist and accumulate in the environment and human beings.

The present study assessed P&B characteristics of LCMs as described by Mackay et al. (49) and Howard et al. (13). Only intensive properties such as degradation half-lives and partition coefficients are meaningfully ranked because they are independent of any consideration of quantity of chemical produced or emitted to the environment. From the systematic evaluation of essentially all 362 commercial LCMs, we demonstrated that over 90% are predicted to be potential P or B chemicals (11). Most of these chemicals have rigid and persistent structures (e.g., diphenyl/triphenyl backbone structure or with halogen substitution) that appear to be persistent and possibly bioaccumulative, similar to POPs including PCBs, PBDEs, and HBCDD (50–53). In addition, we found that 17 of the 33 identified LCMs from 6 models of largely produced LCD devices were detected in indoor dust samples, and most of these were fluorinated and estimated to be bioaccumulative and persistent. Overall, these findings raise concerns regarding the environmental behavior, fate, and adverse effects of LCMs (11) and suggest that future studies on this unique class of chemicals are warranted.

Materials and Methods

Database for the Evaluation of the P&B Properties of LCMs. To address the question of how many LCMs are currently being produced, we surveyed 18 LCM-producing industries in China and compiled lists of all their commercial LCM products from their official websites. A product list containing 362 commercial LCMs was used to compile chemical properties and make assessments of individual LCMs (SI Appendix, Table S1). Since some of the chemicals have no CASRNs, LCMs were entered into the database using Simplified Molecular Input Line Entry Specification (SMILES) notations. Physical–chemical properties were estimated using EPI Suite software (18). Parameters used to make predictions of characteristics used to screen for P&B were CASRN, chemical name, molecular mass, vapor pressure (VP), AO $t_{1/2}$ (atmospheric oxidation half-life) (AOPWIN), $\log K_{aw}$ (air–water partition coefficients), $\log K_{ow}$ (octanol–water partition coefficients) (KOWWIN), $\log K_{oa}$ (octanol–air partition coefficients) (KOAWIN), BCF, BOWIN¹ and BOWIN⁵ (2 biodegradation estimates), and degradation half-lives ($t_{1/2}$) in water, soil, and sediment (fugacity). The properties that were relevant to the determination of P&B included $\log K_{ow}$, BCF, and BOWIN¹ and BOWIN⁵. Once the properties were estimated and added to the database, they were used to rank potential P&B chemicals. We used EPI Suite software (18) to estimate physical–chemical properties of LCMs, such as octanol–water partition coefficients ($\log K_{ow}$) and biodegradation half-lives in environmental media ($t_{1/2}$); the software has been well studied and has been reviewed by Ng et al. (54). The training datasets of EPI Suite software (18) contained biphenyls, esters, nitriles, alkynes, halobenzenes, etc., and therefore, the main structures of the LCMs studied are within the applicability domain of EPI Suite.

Software Used to Predict P&B Properties of LCMs. Molecular structures, SMILES notations, CASRNs, and names of the LCM products were obtained from Cambridge Soft Corporation ChemDraw (55) and the Royal Society of Chemistry ChemSpider database (56). EPI Suite software, developed by the US EPA and Syracuse Research Corp., was used for estimation of physical–chemical properties and environmental fate of 362 LCMs (18). EPI Suite uses 11 separate linear–free energy relationships to estimate properties from first and second principles. A plot of comparisons to typical POPs was generated by R software (version 3.5.1). EPI Suite software and R software are open source and available free of cost.

Preparation of LCM Mixtures. LCD panels of 6 frequently used smartphone models used in the present study were purchased from local smartphone maintenance shops in Nanjing, Jiangsu province, eastern China. Production volumes in China during 2018 of all these brands of smartphones were reported to be greater than 100 million units (57). LCD panels were brought into our laboratory and dismantled manually (SI Appendix, Fig. S1). LCM layers between polarizers in LCD devices were dissolved with acetone and washed into a 500-mL precleaned beaker, then transferred into a 15-mL disposable borosilicate glass tube (16 × 100 mm; VWR International). Then, solvent containing LCMs was blown down to dryness by use of a gentle stream of high-purity nitrogen and then redissolved in 1 mL acetone. To help ensure complete isolation of LCMs from LCD devices, dissolutions were repeated a second time. Results demonstrated that more than 90% of LCMs were isolated from LCD devices by the first dissolution. LCM mixtures were stored at -20 °C until further instrumental analysis (solvent exchanged with 2,2,4-trimethyl pentane [TMP]) or toxicity assessment (solvent exchanged with dimethyl sulfoxide [DMSO]).

Preparation of CEHs. Detailed information on the preparation of CEHs can be found elsewhere (58, 59). Briefly, fertilized and unincubated eggs of white leghorn chicken (*Gallus gallus domesticus*) were purchased from the Canadian Food Inspection Agency and incubated at 37.5 °C for 19 d. Day 19 embryos were rapidly decapitated, and livers were removed and pooled in culture dishes. Hepatocytes were separated and cell aggregations reduced with Percoll and DNase I, respectively. Cells were centrifuged and suspended in fresh medium containing 1 μ g/mL of insulin and thyroxine. Cell suspensions were distributed into 48-well plates (25 μ L cell suspension into 500 μ L fresh medium). Plates were incubated at 37.5 °C under an atmosphere containing 5% CO₂ for 24 h prior to chemical administration. To determine the dose–response relationships for viability of CEHs, after 24 h, they were dosed with the DMSO solvent control (2.5 μ L/well; $n = 3$) or mixtures of LCMs at nominal concentrations of 2, 1, 0.5, 0.25, 0.125, or 0.0625 units per mL (note that 1 unit represents the amount of LCM mixture that was dissolved from 1 in. of LCD devices). For toxicogenomic evaluation using the avian ToxChip PCR array or targeted real-time PCR, a nominal concentration of 2 units per mL was used. Following dosing, cells were incubated for an additional 24 h.

Identification of Chemical Structures of 33 LCMs in LCM Mixtures. Identification of the chemical structure of the LCMs followed the procedures summarized in *Identification of Chemical Structures of LCMs in Current-Use LCD Devices*. First, LCMs in mixtures from LCD devices were screened in full scan mode with a scan range of mass-to-charge ratio (m/z) 50 to 650 by use of a ThermoFisher Scientific Trace 1300 GC coupled with an ISQ LT single quadrupole mass analyzer (GC-MS; ThermoFisher Scientific). The GC-MS was equipped with a DB-5HT column (15 m × 250 μ m × 0.10 μ m; J&W Scientific). The GC temperature ramp started from 80 °C, hold 3 min, ramp 20 °C/min to 160 °C, hold 1 min, ramp 10 °C/min to 240 °C, hold 3 min, ramp 10 °C/min to 300 °C, hold 10 min. The injection volume was 1 μ L. Ultrahigh-purity helium was used as the carrier gas at a flow rate of 1.2 mL min⁻¹. Ionization was operated in heated EI mode. The MS transfer line temperature was set at 300 °C. The ion source temperature was 230 °C.

After mass spectra were acquired for all LCMs, chemical structures were elucidated following previous publications. Specifically, Leclercq et al. reported mass spectra of various classes of LCM (35–39). By analyzing mass spectra, MS fragmentation pathways of LCMs were determined. By combining MS fragmentation pathways, similar to Leclercq and coworkers, with fundamentals of mass spectrometry, structures of LCMs corresponding to each peak of the gas chromatogram were proposed. Structures were further verified by comparing to structures of LCMs that had been established previously. As a result, 33 LCMs were positively identified for subsequent examination in $n = 6$ currently produced LCD devices.

For full identification of LCMs, the ideal way would be to obtain pure authentic standards for comparison of retention times and/or mass spectra. However, only 10 of the 33 LCMs are commercially available as pure standards. These were 4'-methyl-4-pentylbiphenyl (CASRN 64835-63-8, purity > 98%), 4-propyl-4'-vinylbicyclohexyl (CASRN 116020-44-1, purity > 98%), 4-[difluoro-(3,4,5-trifluorophenoxy)-methyl]-3,5-difluoro-4'-propylbiphenyl (CASRN 303186-20-1, purity > 98%), 1-ethoxy-2,3-difluoro-4-(4-propylcyclohexyl) benzene (CASRN 174350-05-1, purity > 98%), 4-propenyl-4'-propylbicyclohexyl (CASRN 279246-65-0), 4'-propyl-4-(p-tolyl)-bicyclohexyl (CASRN 84656-75-7, > 98%), 4-ethyl-4'-(4-propylcyclohexyl)-biphenyl (CASRN 84540-37-4, purity 98%), 1-methoxy-4-(4-propylcyclohexyl)cyclohexane (CASRN 97398-80-6), 4-(4-methylphenyl)-4'-vinylbicyclohexyl (CASRN 155041-85-3, purity 98%), and 4'-ethyl-2'-fluoro-4-propyl-1,1':4',1''-terphenyl (CASRN 95759-44-7, > 99%). These authentic,

native standards were purchased from Tokyo Chemical Industry Co., Ltd. (TCI), J&K (Acceleration Scientific and Industrial Development Thereby Serving Humanity), or Beijing Bayi Space LCD Technology Co., Ltd. For the 10 LCMs where we had authentic standards, their high-resolution molecular weights were confirmed by use of a Q Exactive Focus quadrupole orbitrap mass spectrometer (ThermoFisher Scientific) equipped with a Dionex UltiMate 3000 UHPLC system (ThermoFisher Scientific). This UHPLC-Q-Orbitrap/MS was equipped with a Hypersil GOLD-C18 Selectivity column (1.9 μm ; 100 mm \times 2.1 mm; ThermoFisher Scientific). The injection volume was 5 μL . Pure water (A) and methanol (B) were used as mobile phases. Initially, 5% of B was increased to 95% in 5 min, then increased to 100% at 7 min and held static for 8 min, followed by a decrease to the initial conditions of 5% of B held for 8 min to allow for equilibration. The rate of flow was 0.40 mL/min. Temperature of the column was maintained at 35 $^{\circ}\text{C}$. The ionization was operated in heated ESI mode. The spray voltage was set at 3.5 kV in positive mode. The ion transfer capillary temperature was set at 320 $^{\circ}\text{C}$, and the probe heater temperature was set at 425 $^{\circ}\text{C}$. Full-scan mode was conducted with a scan range of m/z 120 to 1,000. The mass spectrometer was controlled by Xcalibur 4.1 software (ThermoFisher Scientific).

Collection of Indoor Dust Samples and Analysis. To identify and quantify LCMs in indoor environments, 53 sampling points in 7 indoor spaces, including laboratory building, hotel, teaching building, dormitory, electronic product maintenance center, residence, and canteen, were established in Nanjing city, eastern China, from which dust was collected during winter of 2018 (November to December). The 53 samples were numbered L1-14, H1-4, T1-12, D1-10, E1-7, R1-4, and C1-2. A whirlwind car dust collector (CARCHAT DIVI-V401) was used to collect samples of dust, which were subsequently sealed in polyethylene zip bags, transported to the laboratory, and then sieved using a 10-mesh sieve to remove larger materials. Sieved dust samples were transferred into precleaned dark brown glass bottles and kept in a refrigerator at -80°C for further analyses.

Sieved dust (50 mg) was mixed with diatomaceous earth (treated at 600 $^{\circ}\text{C}$ for 8 h) and extracted by ASE (DIONEX 350; ThermoFisher Scientific) with an organic phase (50:50 cyclohexane:ethyl acetate). Oven temperature was 100 $^{\circ}\text{C}$, and pressure was 1,500 psi. ASE extracts were concentrated to 1 mL by use of a gentle stream of nitrogen. To remove obvious impurities, samples were transferred into a glass column, coupled with a Syringe Filter (13 mm \times 0.22 μm , PTFE membrane; ANPEL). Each sample was collected into a centrifuge tube, the solvent removed by evaporation to dryness, and then reconstituted in 7 mL of 50:50 cyclohexane:ethyl acetate. The extract was subjected to gel permeation chromatography (AutoClean GPC; LabTech) that was operated using 50:50 cyclohexane:ethyl acetate at a flow rate of 5 mL/min. The collected fraction was reevaporated to ~ 0.5 mL and further cleaned-up on an Si SPE cartridge (500 mg \times 6 mL; CNW Technologies). The fraction was collected and evaporated to dryness, then dissolved into 200 μL of TMP and transferred to a glass GC vial with insert and cap, and stored at 4 $^{\circ}\text{C}$ until GC-MS/MS analysis.

The analytical instrument was a ThermoFisher Scientific Trace1300 GC, coupled with a TSQ 9000 triple-quadrupole mass spectrometer (ThermoFisher

Scientific). The GC column used for separation was TG-SQC (15 m \times 0.25 mm \times 0.25 μm) (ThermoFisher Scientific). A volume of 1 μL of sample was injected, split-less with an injector temperature of 285 $^{\circ}\text{C}$. Helium was used as the carrier gas with a constant flow rate of 1.0 mL/min. Oven temperature was programmed as follows: the initial temperature was held at 80 $^{\circ}\text{C}$ for 3 min, 20 $^{\circ}\text{C}/\text{min}$ to 120 $^{\circ}\text{C}$, 5 $^{\circ}\text{C}/\text{min}$ to 280 $^{\circ}\text{C}$ (held for 1 min), and then ramped to 300 $^{\circ}\text{C}$ at 10 $^{\circ}\text{C}/\text{min}$ and held for 3 min. Mass spectrometer parameters were as follows: the ion source temperature and transfer line temperature were 280 $^{\circ}\text{C}$ and 290 $^{\circ}\text{C}$, respectively, and the ion source filament voltage was 70 eV. The mass spectrometer was operated in the EI mode, and analysis was performed in selected-reaction monitoring mode.

Data Availability Statement. More details on experimental procedures and datasets can be found in *SI Appendix*, which includes 9 supporting figures and 5 supporting tables. The supporting figures and tables contain detailed information on persistence, bioaccumulation, and toxicity data for 362 commercial LCMs (*SI Appendix, Table S1*); predicted properties of 10 LCMs that were identified to be vPvB in the environment (*SI Appendix, Table S2*); RefSeq accession numbers and gene descriptions for the 43 target genes and 2 housekeeping genes on the fourth generation Avian ToxChip PCR array (*SI Appendix, Table S3*); relative abundances of characteristic ions in the EI mass spectra of LCMs in the LCDs of 6 models of largely produced commercial smartphones (*SI Appendix, Tables S4–S6*); property data for the 33 LCMs that were identified from the LCDs of 6 models of largely produced commercial smartphones (*SI Appendix, Table S7*); ion pairs and collision energy, spiked recoveries, and validation parameters for determination of individual LCMs (*SI Appendix, Table S8*); limit of detection, blank concentration, detected frequency, arithmetic means, and ranges (ng/mL) of LCMs in indoor dust samples (*SI Appendix, Table S9*); collection of LCMs from LCD devices in the laboratory (*SI Appendix, Fig. S1*); distribution of manufacturers of LCs and LCDs in the world (*SI Appendix, Fig. S2*) and China (*SI Appendix, Fig. S3*); the possible fragmentation pathways of LCMs in LCDs from 6 models of largely produced commercial smartphones under electron impact ionization (EI) source (*SI Appendix, Fig. S4*); and total ion chromatogram of the LCM mixtures from 6 dismantled LCDs devices by use of GC-EI-MS (full scan mode) (*SI Appendix, Fig. S5*).

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