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Bioassay guided analysis coupled with non-target chemical screening in polyethylene plastic shopping bag fragments after exposure to simulated gastric juice of Fish



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GRAPHICAL ABSTRACT



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In this study, fragments of polyethylene plastic bags were treated with simulated gastric juice of fish for 16 h. Following solid-phase extraction, methanol eluents caused acute toxicity to embryos and larvae of Japanese medaka. Chromatographic fractions (polar to more non-polar with numbers increasing) of the extract were evaluated for toxicity and estrogenic activity using medaka and an estrogen receptor (ER) cell-line. Fractions 6 and 9 had the highest estrogenic effects with relative hydrophobic chemicals. The *vtg* expression in fraction 6 was 22-fold higher than control, and the ER cellular response in fraction 9 was 8.5-fold higher than controls. Following non-target screening (NTS), several novel phthalates and phenols were identified in the above two fractions. Fractions 1 and 2 appeared to be primarily responsible for the acute toxicity observed with the whole extract. The hatching rate decreased to 36 % in fraction 2, and was not observed following exposure to fraction 1. NTS of these fractions indicated 635 and 808 entities, respectively, most without toxicity information. These

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Received 5 April 2020; Received in revised form 2 July 2020; Accepted 5 July 2020 Available online 08 July 2020 0304-3894/ © 2020 Elsevier B.V. All rights reserved. results indicate plastic leachates from gastric juices of fish are complex mixtures of many compounds that can have acute reproductive and sublethal endocrine impacts in fish.

1. Introduction

In 2017, annual plastic production (348 million tons) surpassed the total mass of human beings on the planet. Plastic packaging constitutes 39.6 % of total plastic production (Steffen et al., 2015; EuropePlastic, 2018). Much of this plastic is transported to surface waters and consumed by wildlife (Menezes et al., 2019; Jabeen et al., 2017; Gatidou et al., 2019; Li et al., 2020; Su et al., 2019). After consumption, gastric digestion has been shown to release numerous additives from the plastic matrix into fluids that are absorbed into the gastrointestinal tracts of biota (Tanaka et al., 2015, 2018; Guo et al., 2020; Liu et al., 2020), and these pollutants may even be transferred to organisms at higher trophic levels (Tanaka et al., 2018).

Various kinds of additives have been detected in plastics, such as plasticizers, bisphenols, as well as persistent bioaccumulative toxic substances (PBTs) (Guo et al., 2020; Zhang et al., 2018; Chen et al., 2019a, 2018; Jang et al., 2016; Chen et al., 2019b). Plasticizers are used for improving the durability and flexibility of polymeric films (Bhunia et al., 2013; Hahladakis et al., 2018). Phthalates, acetyltributyl citrate, and heptyl adipate are all widely used plasticizers (Sablani and Rahman, 2007). Antioxidants are also commonly used in plastic packaging, which are embedded to delay the oxidative degradation induced by reactive free radicals that are generated under light, heat, or mechanical abrasion (Bhunia et al., 2013; Sablani and Rahman, 2007). Typical antioxidants include arylamines, phenolics, and organophosphites, such as bisphenol A (BPA), Irgafos, Irganox, Cyanox series (Bhunia et al., 2013; Kattas et al., 2000). Other known constituents of plastics include colorant pigments, heat stabilizers, slip agents, residual, and unreacted oligomers (Hahladakis et al., 2018).

The most commonly used plasticizers and antioxidants in polyethylene are phthalates, adipate, BPA, DEHA, and alkylphenols, whose migration has been widely documented in literature (Beldi et al., 2012; Fasano et al., 2012; Jeon et al., 2007). Moreover, polyethylene has been widely used to produce shopping bags, and many studies have reported that their embedded additives can leach out under different conditions (Suhrhoff and Scholz-Böttcher, 2016; Mattila et al., 2011; Alam et al., 2018; Simoneit et al., 2005). Previous studies have reported that the detected additive and oligomer amounts reach 0.1 - 0.23% of the mass of polyethylene shopping bags with multiple compounds detected (Suhrhoff and Scholz-Böttcher, 2016; Simoneit et al., 2005). Examples include phthalates, Irgafos 168 and 1076, tris(2,4-di-tert-butylphenyl) phosphate, chain n-alkanes, acetyl tri-n-butyl citrate, dehydroabietic acid, heavy metals, organometallic compounds, and many additives' oxidation and degradation products (Suhrhoff and Scholz-Böttcher, 2016; Alam et al., 2018; Simoneit et al., 2005).

Plastic additives have been shown to have multiple adverse effects on marine organisms (Hermabessiere et al., 2017; Guo and Wang, 2019). Many additives, such as phenols and phthalates, have been shown to mimic estrogen and disrupt endocrine pathways in wildlife (Olujimi et al., 2010; Boas et al., 2012). Given the diversity of plastic items and their constituents, not all plastic items have the same levels or types of additives. In a previous study, our results showed that polyethylene plastic bag leachates from simulated bird and fish gastric juices had the highest concentrations of 12 additives targeted for chemical analysis and exhibited the highest estrogen receptor activity among 16 plastic items commonly found in natural organisms (Coffin et al., 2019). When comparing the estrogenic activities predicted from the quantified targeted chemicals with the real biological activities, only 17 % of the activity contribution can be explained (Coffin et al., 2019), suggesting that additional chemicals with estrogen ligand activities were present in the leachate. According to Groh et al. (2019), at least 906 likely chemicals and 3377 possible chemicals have been reported to be present on plastic packaging (Groh et al., 2019).

The combination of effects directed analyses (EDA) with non-target screening (NTS) has been shown to identify causative toxic agents in extracts of surface water, wastewater effluents, and sediments (Brack et al., 2007, 2018). In the current study, we chromatographically separated simulated gastric fluid leachates of polyethylene shopping bag fragments into fractions. Sequentially, the whole extract and the fractions underwent *in vivo* and *in vitro* evaluations for estrogenic activity and acute toxicity. Biologically active fractions then underwent NTS to identify chemical constituents. Results indicate complex mixtures of multiple novel compounds without toxicological evaluation may contribute to the biological effects previously observed with this specific type of plastic.

2. Materials and methods

2.1. Chemicals and materials

Sea salt was purchased from the Instant Ocean (Spectrum, USA). Shopping plastic bags were bought from a local supermarket (reusable type, USA). All other chemical reagents used in the study were of analytical grade (Sigma-Aldrich, USA). All the glassware were thoroughly rinsed with methanol three times to avoid organic contamination and then rinsed by Milli-Q water and dried at 60 °C before use. Procedural blanks were conducted in parallel throughout the process.

2.2. Organisms and cells used for bioassays

Japanese medaka (*Oryzias latipes*) was used to screen plastic leachate toxicity in the present study. The medaka was cultured at the University of California, Riverside (AUP # 20,140,002), and housed in medium-hard water at 28 °C with a photoperiod of 14:10 h of light: dark. Fish adults were fed twice daily with brine shrimp (*Artemia nauplii*), and experimental embryos were collected before 4 hpf (Coffin et al., 2018). Human breast carcinomaVm7Luc4E2 (ER) cells were donated by Dr. Michael Denison (University of California, Davis). The cells were incubated in the ER growth media of Roswell Park Memorial Institute (RPMI)-1640 (Mediatech Inc., USA) and 10 % dialyzed fetal bovine serum (Invitrogen, USA) at 37 °C before assay. The assay media was phenol-red free Dulbecco's minimum essential medium with 5% charcoal-stripped fetal bovine serum and 2% Glutamax (Sigma-Aldrich, USA) (Coffin et al., 2019).

2.3. Polyethylene plastic packaging fragment digestion and leachates separation

White colored polyethylene plastic bags were bought from a local supermarket, and the composition was identified as polyethylene using Fourier Transform Infrared spectroscopy (FTIR) with a matching rate > 70 % (Nicolet iN10, Thermal Fisher Scientific, USA) (Fig. S1A). Meanwhile, we also found one additive, calcium carbonate, on the plastic surface (Fig. S1B). This additive is usually used as a pigment or modifier embedded in plastics (Murphy, 2001).

Since previous studies indicated simulated fish digestive leachate from this item possessed significant biological and chemical activities for the estrogen receptor, similar methods were used in this study (Bigg, 1985; Jackson et al., 1987). In brief, 2 g of pepsin, 32 g of sea salt were added into 1 L of Milli-Q water in a glass container. Then, shopping plastic bags (Fig. S2) were arbitrarily cut into small square fragments (\sim 5 cm length) and put into a glass container. Next, the containers were shaken at 100 rpm (1575 R, VWR Scientific, USA) at 28 °C for 16 h (to simulate fish gut retention time) (Turner et al., 2001).

The amount of plastic fragments used in 1 L extraction solution was 7 g (0.007 g/g). The reported plastic mass concentration in fish samples was 5 \pm 8 mg for *Symbolophorus californiensis* (Boerger et al., 2010). The gastrointestinal (GI) tract of fish usually falls in the range of 9–14 % of body weight (Ray and Ringø, 2014). The calculated weight of *S. californiensis* was around 10 g according to its length (Length-Weight relationship for Symbolophorus californiensis, 2020). Thus, the estimated plastic concentration in fish is approximately 0.005 \pm 0.007 g/g, which has a similar plastic burden to that used in the present study.

2.4. SPE extraction and RP-HPLC fractionation for plastic extracts

Solid-Phase Extraction (SPE) was used to remove and concentrate additives from the plastic leachates from the simulated gastric juice. Sep-Pak C18 cartridges (6cc (1 g), Waters, USA) were rinsed with 10 mL of methanol and then conditioned with 10 mL of Milli-Q water. Then, each cartridge was loaded with 500 mL of the plastic leachate samples with a flow rate of one drop per second. The cartridges were later washed with Milli-Q water and then eluted with 8 mL of methanol at a flow rate of one drop per 3 s. Finally, two cartridge samples were pooled as one sample, and the extracts were blown to dryness with nitrogen gas and resuspended in methanol. These methanol samples were then separated into two parts: one-tenth was replaced by dimethyl sulfoxide (DMSO) for bioassay analysis, and the leftover remained in methanol for chemical fractionation and quantification.

For the chemical fractionation, the extract from SPE underwent separation using High-Performance Liquid chromatographic Chromatography (HPLC, LC-2030, Prominence-i, Shimadzu, Japan) coupled with a Fractionation Collector (CF-1, Spectra/Chrom, Fisher Scientific). Plastic extracts (40 µL) were injected into a C18 column (4.6 mm I.D. \times 150 mm, Shiseido, Japan), according to Reineke et al. (Reineke et al., 2002) with modifications. The plastic leachate samples were separated using an isocratic solvent mixture of 50 % water and 50 % methanol over 30 min. A 50 % mixture was arbitrarily based on previous studies with sediment extracts (Schlenk et al., 2005) and wastewater extracts (Sapozhnikova et al., 2005). Fractions were collected every 3 min, with a flow of 1 mL/min resulting in ten fractions. The column temperature was 40 °C. For the subfractionation of fraction 1 and fraction 2, the same HPLC program was used, but fractions were taken every 60 s, resulting in three subfractions per fraction. All the fractions and subfractions were blown to the water phase, and the same volumes of mobile phase (50 % water and 50 % methanol) were collected as solvent control. Based on biological activities, three fourth of the samples were used for bioassay analysis, and the remaining one fourth of the sample was evaporated under nitrogen gas with temperature below 40 °C to dryness for further chemical analysis.

2.5. Plastic extract fractions toxicity to medaka embryos and larvae

For the plastic extract fractions toxicity studies, ten healthy fertilized embryos were selected and transferred to Petri-dishes for exposure, and the final concentration was $1 \times$ (relative to ambient concentration). The mortality percentage and heartbeat rate of embryos were recorded after 4 day post fertilization (dpf) and 5dpf for each subfraction (Fig. S3) or fraction. The hatching rate of medaka larvae was recorded after 10 dpf. All exposure solutions were aerated to reach oxygen saturation and replaced 80 % daily.

2.6. Fish mRNA expression analysis

The development status of medaka embryos and larvae were observed with an inverse microscope (SZH10, Olympus, Japan). The hatched medaka larvae were continually exposed until 14 dpf with different plastic leachate fractionation solutions, along with negative control, solvent control, and positive control (containing 500 ng/L of 17-beta estradiol). On the last day of exposure, the fish were anesthetized with 1 g/L MS-222, and their whole bodies were flash-frozen in liquid nitrogen and stored at -80 °C until mRNA analysis.

Quantitative reverse transcriptase-polymerase chain reaction (q-RT-PCR) was carried out according to a previously described method (Braunig et al., 2015). First, RNA was extracted from the whole body of Japanese medaka larvae using an RNeasy Mini Kit (Qiagen, Germany). The RNA quality was assessed by the 260/280 nm ratio on a Nanodrop spectrophotometer and verified by its appearance on 1% agarose-formaldehvde gels. For each sample, the cDNA was synthesized from 200 ng/mL of RNA using a reverse transcription system kit following the manufacturer's instruction (Promega, USA). The primer sequences of the target genes of vtg, and the reference gene of β -actin were designed using the gene bank of NCBI (Table S1), and each gene was tested in three replicates and repeated three times. The reverse PCR experiment was performed as follows: the amplification reaction mixture contained reverse transcription product 1 µL, SybGreen PCR mix 8 µL, each primer (10 pmol/ μ L) 1 μ L, and ultrapure water 5 μ L. The reaction mixture underwent 2 min at 95 °C followed by 40 cycles of 10 s at 95 °C, and 30 s at 60 °C, and 5 s at 54 °C in a thermal cycler (CFX-6, Bio-Rad, USA). Fold changes were determined using $2^{\triangle \triangle Ct}$ and normalized the β -actin transcript levels.

2.7. ER bioassay

Cell viability was assessed using the 3-(4,5-dimethylthiazd-2-yl)-2,5- diphenyltetrazolium bromide (MTT) bioassay (Van Meerloo et al., 2011). Sample concentrations that elicited 80 % survival or greater inwell were deemed acceptable for receptor-binding activity measurements. The performance of the ER assay has been explained in detail in a previous study (Coffin et al., 2018). ER cells were then plated at a concentration of 2 \times 10⁴ cells/ 100 μL in 96-well plates and incubated at 37 $^\circ\text{C}$ for 24 h. Then, 10 μL of the leachate in DMEM was added in triplicate at several concentrations, ranging from $1 \times$ to $50 \times$ (relative to the ambient concentration before SPE) and incubated for 24 h. Cells were lysed, and the luciferase activity of cells was measured in a luminometer with automatic injection of 50 µL of luciferase assay reagent to each well. The relative light units measured were compared to the E2 standard curve following background activity subtraction. The EC₅₀ of the positive control 17-beta-estradiol was 6.3 ng/L (22.98 pM). The Limit of Detection was 0.64 ng/L, and the Limit of Quantification was 1.28 ng/L.

2.8. Non-target screening

All extracts were diluted to $100 \times$ with methanol and analyzed in three technical replicates. Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS) analysis was conducted on both positive and negative ionization modes with samples analyzed in random order on an Agilent 1290 Infinity II LC and a 6550 Q-TOF instrument. The separation was performed on an Agilent InfinityLab Poroshell 120 EC-C18, 2.1 \times 100 mm, 1.9 μ m column, with a 0.4 mL/min mobile phase flow, detailed conditions are provided on Table S2. Components were grouped and extracted according to respective ion clusters with a threshold abundance of 20,000 counts for peak identification using Agilent MassHunter Workstation Profinder (version 10.0). Statistical analysis and data interpretation were made using Agilent MassHunter Workstation Mass Profiler Professional (version 15.1). Potential EDC's and other potential additives were screened against available personal compound database and library (PCDL) for extractables and leachables that includes: (1) stabilizers, accelerators, intermediates, residual monomers, phthalates, lubricants, slip agents, photoinitiators, plasticizers, dyes, and cosmetic additives; (2) antioxidants, UV stabilizers and

their breakdown or degradation products; (3) food packaging contaminants and printing ink components and their breakdown or degradation products; (4) PFCs, PAHs, nitrosamines, and silicones. Tentative identification was achieved through a tiered workflow that considers different identification confidence levels (Schymanski et al., 2014). Probable structures were assigned by library spectrum match and diagnostic evidence (MS/MS) data generated by all ions fragmentation. Accurate mass error (ppm) of less than +/- 5 ppm, library match score > 85 (related to isotopic cluster distribution, number of assigned ions, observable adducts, accurate mass difference) and presence of all ions MS/MS fragmentation pattern were established as probable structure assignment criteria. Digestion and extraction procedural controls and instrument blanks were analyzed using the same procedures. Entities present both in samples (Fig. S4) with an abundance fold change of < 5 than procedural controls were excluded from data analysis.

For semi-quantitative analysis of identified entities, peak areas were normalized by reference mass ion intensities to account for possible ion suppression/enhancement and are presented as parts per thousand (‰) of total areas of all fractions (Table S3&S4).

2.9. Statistics

Statistical analysis was performed by using SPSS software (version 20.0, IBM, USA). The data were first verified for normality with the Shapiro-Wilk method and then compared by the one-way analysis of variance (ANOVA), and significant differences were indicated by using Duncan's multiple range test with $\alpha = 0.05$. Data are presented as mean \pm SEM. Data with * represents p < 0.05 vs. the control values, and the bars with different letters mean they are statistically different from each other (p < 0.05).

3. Results and discussion

3.1. Estrogenic activity in different plastic leachate fractions

The estrogenic activity (EA) value of the unfractionated plastic extract in the ER assay was significantly higher than that of control (equivalent to 0.94 ± 0.28 ng/L E2, p = 0.028) (Fig. 1). This result is in accordance with our former study that showed plastic bag extracts also had EA after simulated gastric digestion, with higher activity than other plastic products (Coffin et al., 2019).

EA was highest in the F9 fraction, which had compounds (listed in the Table S3) of an approximate LogKow of 6.1. The LogKow value for F9 was an average value for all the detected compounds in the F9 fraction (the LogKow values for chemicals were obtained from the PubChem database (PubChem, 2020). Estradiol equivalent value for the F9 fraction was 1.46 ± 0.11 ng/L E2 in the ER assay, which was significantly higher than that of other fractions, including the negative



control. Similarly, vtg mRNA expression in the medaka larvae was 8.5 fold higher than that of the negative control (p = 0.4). With NTS methodology, we found that the F9 fraction contained 34 entities, including five phthalates; pentyl isopentyl phthalate (PIPP), diheptyl phthalate (DHEPP), dihexyl phthalate (DHP), 2-ethylhexyl hexyl phthalate (HEHP), and butyl octyl phthalate (BOP) (Table S3). DHP is a commercial phthalate ester with an estrogenic activity of 1 nM (Williams et al., 2017). HEHP is a monomer of DEHP, which has been reported to be one of the most widely used plasticizers in the international plastics industry (Erythropel et al., 2014; Chen et al., 2014). Two phenols (bisphenol G and 2,3-dioctylphenol) and 2-ethylhexyl benzoate were identified in the F9. The EC₁₀ value of bisphenol G was shown to be 1.9 E-05 M in the estrogenic Yeast Estrogen Screen (YES) assay, and 2,3-Dioctylphenol may also have estrogenic activity, but affinity values were not known (Dvorakova et al., 2018; R.T., 2007). Other UV absorbers, antioxidants, and intermediates and their estrogenic effects are provided in Table 1.

Overall, in the F9 fraction, several novel alkylphenols and phthalates were detected by the NTS. But some other compounds present in this fraction may also exert endocrine disrupting effects. For example, some UV absorbents and antioxidants that may also have slight estrogenic effects according to the Toxcast model (Williams et al., 2017) (Table 1). Additional studies are needed to characterize the identified compounds and determine the concentrations needed to generate estrogenic effects. The diversity of probable structures assigned in each fraction can be partly attributed to the presence of non-intentionally added substances (NIAS), that constitute a group of chemicals not directly applied but introduced or formed during the production process (Martínez-Bueno et al., 2017). The plastic bag used in this study contains at least 20 % of recycled polyethylene plastic as marked on the bags, and the plastic recycling process can bring in many other pollutants.

Unlike F9, the estrogenic effects in F6 were mainly reflected in the in vivo assay. Expression of vtg transcripts in medaka larvae showed significant upregulation (22-fold) in the F6 fraction compared to the negative control. However, the in vitro ER assay had limited activity in the F6 fraction (Fig. 1). Through NTS, 65 entities were found in the F6 fraction (Table S3). Among the identified chemicals, the antimicrobial agent terbuthylazine (TERBA) and the antioxidant 2,5-di-tert-butylbenzoquinone were shown to have AC50 values of 3.18 and 21.03 nM in the in vitro ERa_LUC_VM7_Agonist assay (Williams et al., 2017), respectively (Table 1). In addition, two phthalic acid ester (PAEs) monomers, namely, monoisononyl phthalate and monoheptyl phthalate were also observed which may be a result of ester degradation. Two other chemicals with ER activation were observed in the F6 fraction (ethoxylated trimethylolpropane triacrylate and hexyl cinnamaldehyde), with AC50 values of 6.75 and 0.00983 nM respectively (Table 1) (Williams et al., 2017; Kjeldsen et al., 2013).

The combination of several estrogenic compounds together may

Fig. 1. In vivo (medaka vtg expression) and in vitro (ER cell proliferation) estrogenic activity responses to the plastic leachate exposure. Grey bars represent the expression fold change with mean ± SEM, and blue bars represent estradiol (E2) equivalent (EEQ) values mean ± SEM. Different letters denote statistically significant differences among groups (p < 0.05) in the *in vivo* assay. Asterisks denote statistically significant differences relative to control (p < 0.05) in the *in vitro* assay. The estrogenic effects of vtg mRNA expression was not obtained in the whole extract and F1 samples, because none of the fish embryos exposed to these groups hatched. Ctrl: negative control; whole: the whole extract of the plastic leachate. F1-10: fractions 1-10.

Table 1

The toxicity levels of identified chemicals having demonstrated estrogenic activity in Toxcast and their LC_{50} values in the T.E.S.T. software (Williams et al., 2017; Martin, 2016). Note: ER α bioassay AC₅₀ values are obtained from the Toxcast database. LC_{50} values are 48 h *Daphnia magna* acute toxicity results acquired from the T.E.S.T. software, which are only used to reflect the acute toxicity of these chemicals. Numbers in italic are real experimental values, and numbers in normal font are prediction values. The color gradation from red-white-blue represents toxicity from high-medium-low. T.E.S.T.: Toxicity Estimation Software Tool.

Gargory checked number logics Fraction AG_00000 Process model (Willing) et al. 2017) 0 phthalace 2.40-Trimechylberzoylphenylphonylmin acid ethyl ester 5.000 FI Inactrice potential 0	Chemicals			Fraction	ERa bioassay		LC ₅₀
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pinhalaceMonoleapy fulnable500F0NA<	phthalate	2,4,6-Trimethylbenzoylphenylphosphinic acid ethyl ester	3.900	F1	inactive	potency	0.0452
pinklakeMade of the Mark (algebraic) persist plankar (algebraic) persist plankar (base)MaNA <th< td=""><td>phthalate</td><td>Monoisononyl phthalate</td><td>5.600</td><td>F6</td><td>NA</td><td>NA</td><td>12.120</td></th<>	phthalate	Monoisononyl phthalate	5.600	F6	NA	NA	12.120
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phthalateDHP / 2Ming/ phthalate (DMXP) (DMP)6.820PNA3phthalateBO/ / Anyl oct] phthalate6.70PNA1baphenolSuphanol9.700PNA1baphenol2.000 reliphonol9.700PNA1baphenol2.000 reliphonol9.700PNA1baphenol2.000 reliphonol9.700PNA1attinicrobialPertor (NA) fondorsh) Na pertoryNAPNANANAattinicrobialPertor (NA) fondorsh) Na pertory3.400P10.800PnathalasNA	phthalate	DHEPP / Diheptyl phthalate (DHP)	8.000	F9	inactive	constant	2.97
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phthalate B0/P huyl oxyl phthalate 6.9 P9 nafew potency path 1 bisphenois 2.3-biscryphenol 9.700 P3 NA 1 bisphenois 2.4-biscryphenol 9.700 P3 NA 6 entimicrobial BT/ Penzion (N-Nometyl-Appenyluron) 1.00 P2 isactive constant 2 antinicrobial Penzion (N-Nometyl-Appenyluron) 3.00 P6 0.057 pathway 1 antinicrobial Technylusiae (TREBA) 3.00 P1.2 very wask potency N antioxidant 2.540 (r/J.5-biert-huylbenzoquinone 3.00 P1.2 N NA 0 antioxidant Disporyl phtylephylanite 3.100 P1.7 NA NA 0 antioxidant NA NA NA NA 0 0 NA NA 0 antioxidant NA N	phthalate	HEHP / 2-Ethylhexyl hexyl phthalate	6.700	F9	NA		3.38
bisphenolsBisphenolsCa.3DiocryphenolC.4DiocryphenolC.4DiocryphenolNANcolorant1.4TOP112InactivepotencyMcolorantTolvinise Bites (Tolvinium)1.4DNANantimicrobialFermion (N.ADinactly) Aphenylurea)3.130P12macriveconstrant2.2catalysi2.4Diochylibiozanthone3.100P12macrivepathway1catalysi2.4Diochylibiozanthone5.100P122macrivepathwayNcatalysi2.5DBQ / 2.5Dirch-tarbuphenzoquinone4.600F1 P2inactivepotencyNantioxidantIzopoyl diphenylamine4.600F1 P3inactivepotencyNantioxidantIsopoyl diphenylamine4.600F1 NNANANANAantioxidantIrgois 184 (Artinoxidant 168)1.500P90.0139pathway2intermediate4.4TE-Baug/cyclobezylarylate4.000F1NANANANAutaremediate4.4TE-Baug/cyclobezylarylate4.000F1NANANANAUV aborbermatrixe 1.12inactiveconstant5.200P9inactiveconstant5.20UV aborbervalue-baug/sylabezcene1.700F2NA <td< td=""><td>phthalate</td><td>BOP / Butyl octyl phthalate</td><td>6.9</td><td>F9</td><td>inactive</td><td>potency</td><td>4.09</td></td<>	phthalate	BOP / Butyl octyl phthalate	6.9	F9	inactive	potency	4.09
bisphenols2.3-Directylphenol9.700PJNAPotencyQcolorant/bisphenols2.4-DirectylphenolNAPINANANANANAcolorant/bisphenols3.100PC2inactiveconstant33NA<	bisphenols	Bisphenol G	6.300	F9	NA		1.11
caloratic biplenoi1.570F1.72incluic potency4antinicrobalBT / Bonizothianolinone3.400F2incluicconstant3antinicrobalBT / Bonizothianolinone3.400F2incluicconstant3antinicrobalFramo (N.A.Vinchyl-Y. Bonizothianolinone3.400F1 F2very vackpotencyNantinicrobal2.4.Dicthylthionanthone4.600F1 F2very vackpotencyNantioxidant2.5.104 (J.2.5.5)5.5.104 (J.2.5.5)1.7.2.6 (J.2.6.5.7.2.7.2.6.5.7.2.7.2.6.5.7.2.7.2.6.5.7.2.7.2.6.5.7.2.7.2.7.5.7.7.2.7.5.7.7.7.7.7.7.7.7	bisphenols	2,3-Dioctylphenol	9.700	F9	NA		0.2
Cator cationIndicate file (1000mill)NANANANANAantimicrobial antimicrobial entimicrobialBit / Actionalization34.00F22inactive 	colorant/bisphenols	2,4-Dinitrophenol	1.670	F1,F2	inactive	potency	4.56
antimicrobial Peruson (N.A.Dinchyl-N.Phenylureo) 3.130 P2 inactive constant 2 antimicrobial Technylazine (TEBA) 3.130 P3 in active constant 2 antimicrobial Technylazine (TEBA) 3.130 P1 P2 inactive constant 1 calayst 2.4.Dischylthiosanthone 1.000 P1 P2 very weak potency N P3 in active 2.4.Dischylthiosanthone 1.000 P1 P2 very weak potency N P3 in active 1.2.Disch 2.5.Dis (7.2.Disch 2.1.Disch 2.1	colorant	Toluidine Blue (Tolonium)	NA	F1	NA	NA	NA
antimicrobia Perton (N, A-Dinff)ris-Paperayutea) 3.130 P2 natrive constant 2 canalyst 2,4Dierhylithioxanthone 3.400 P6 0.87 pathway 1 canalyst 2,5DB0 (2,25)-tett-burylbenzoquinone 4.600 F1 P2 inactive potency N antioxidant Laporpyl dipherylamine 4.600 F1 NA NA 0 antioxidant Laporpyl dipherylamine 3.130 P9 0.0139 pathway 2 antioxidant Lagoia 16 (Antioxidant 166) 3.130 P9 0.0139 pathway 2 intermediate 4.tett haryle hydroxyminole (2-ter-Buryl-4-methoxyphenol) 3.200 P3 0.040 pathway 2 intermediate A.55 Trinnorphydrophoteconone (Lophrone) 1.700 F2 inactive onathway 6 intermediate Authraginone 3.500 P9 1.200 calinhaway 1 UV aborber Timini 1.130 A A00 pathway 1 UV aborber <td>antimicrobial</td> <td>BIT / Benzisothiazolinone</td> <td>3.400</td> <td>F2</td> <td>inactive</td> <td>constant</td> <td>32.68</td>	antimicrobial	BIT / Benzisothiazolinone	3.400	F2	inactive	constant	32.68
antimicroDatalIPS0.005/pathway1canalyst2.4.7.10er/thitosanthone5.100P1 P.2very veakpotencyNcanalyst2.5.200 / 2.5.10er.thug/bacquinone4.600P1 P.2.47.67.92.033Hill3antioxidiant2.5.200 / 2.5.10er.thug/bacquinone3.600P1 P.2.27.67.9A.66.Hill3antioxidiantPOPPH / A.finzondphenylamize3.130P1P1.22NNNNantioxidiantHDPH / A.finzondphenylamize1.500P30.013pathway2NantioxidiantHIA / 3.74.71.10y1.500P40.018pathway2NantioxidiantHIA / 3.74.71.10y1.700P1NANANNintermediateAminocaproce acid-2.950P1.72InactivepotencyNintermediateAminocaproce acid3.300P91.2050Gain-loss2UV aborberPalimine A4.700P2NANAN1UV aborberPalimine A4.700P2NANAN1UV aborberPalimine A2.300P1.22inactiveconstant0.60UV aborberPalimine A1.300P1.22inactiveconstant0Others1.3016/group/blenzne4.500P1.22NANANANOthers1.3016/group/blenzne1.300P1.22NANANANANAO	antimicrobial	Fenuron (N,N-Dimethyl-N-phenylurea)	3.130	F2	inactive	constant	29.95
	antimicrobial	Terbuthylazine (TERBA)	3.400	F6	0.057	pathway	11.040
catalyst2-followitosanthone4.600FI /2inactivepotencyNNNNanticoxidantSp.500 / 2.50-iert-burgh-lynine4.600FINA	catalyst	2,4-Diethylthioxanthone	5.100	F1 F2	very weak active	potency	NA
antioxidant 2.5-D80 / 2.5-Die (r-burylbenzoquinone 3.000 F12 NA NA NA antioxidant NDPHA / Nitrosodiphenylamine 3.00 F12 NA NA NA antioxidant Irgafos 166 (Antioxidant 168) 15.500 F9 inactive potency N antioxidant BHA / 5-Tert-buryl-4-hydroxyanisol (2-tert-Buryl-4-methoxyphenol) 3.000 F1 NA NA NA intermediate Antinocaproiz acid -2.950 F12 inactive potency 3 intermediate Barcophenone 3.05 F10 NA NA NA intermediate Anthraquinone 3.00 F9 inactive constant 1. UV aborber Touvin 1130 4.00 F9 inactive constant 5. UV aborber Padimate A 5.300 F9.2 inactive constant 5. UV aborber Padimate A 5.300 F9.2 NA NA NA others 1.4562(4.20me	catalyst	2-Chlorthioxanthone	4.600	F1 F2	inactive	potency	NA
antioxidant isopropri diphenylamine 4.600 F1 NA NA NA NA antioxidant Irgafos 168 (Antioxidant 168) 15.500 P1.22 42.65 Hill 7. antioxidant BH A/ 57ret-buyl 4-Mythoyanislo (2-ter-Buyl-4-methoxypheno) 3.200 P9 0.0139 pathway 2. intermediate Arminocaprovic aid -2550 P1.22 inactive potney 3. intermediate Aminocaprovic aid -2500 P1.22 inactive constant 1. intermediate Aminocaprovic aid -2500 P1.22 inactive constant 1. V1 aboorber Benzophenone 3.300 P9 6.810 Hill 4 V1 aboorber Tawin functoxycinnamate 4.300 P1.22 inactive constant 0. others 1.450it50/copythenzene 4.500 P1.22 inactive constant 0. others 2.450/copythenzene 4.500 P1.22 inactive potens 0. <	antioxidant	2,5-DBQ / 2,5-Di-tert-butylbenzoquínone	3.400	F1,F2,F6,F9	21.03	Hill	3.56
antioxidant NPHA / Nitrosodiphenylamine 3.130 PI,22 42.65 Hill 7 antioxidant IFAgA / 3Fert-buryl-4-hydroxyanisole (2-tert-Buryl-4-methoxyphenol) 3.200 P9 0.0139 pathway 2 intermediate Atter-Buryl-Schwarone (1500) 1.700 F1 NA NA N intermediate Anthraquinoe -2.950 P1.22 inactive oonstant I. intermediate Anthraquinoe 3.30 P9 1.2.050 Gain-loss 2 UV aborber Trunvin 1130 4.700 F2 inacrive constant 5 UV aborber Padimate A 4.300 P9 inacrive constant 5 UV aborber Polytometoximamate 5.300 P9 inacrive constant 5 UV aborber 2-Naphtylylamine 2.500 F1.F2 NA NA N others 3-Antinacetophenone 0.600 F1.F2 NA NA 2 others 2-Antinocacetophe	antioxidant	Isopropyl diphenylamine	4.600	F1	NA	NA	0.84
antioxidant IP30 inactive petnery N antioxidant BHA / 3177-bityl-4-hydroxyansiole (24ref-Butyl-4-methoxyphenol) 3.200 F9 inactive petnery N intermediate 4-tert-Butyl-cyclobasenone (Isophorone) 1.700 F1 NA NA N intermediate 3.55-Trimethyleyclobasenone (Isophorone) 1.700 F2 inactive constant I UV absorber Padimate A Antinocayticobasenone (Isophorone) 3.300 F9 1.0500 Gain-loss 2 UV absorber Tadimate A 4.300 F9 6.810 Hill 3 UV absorber Padimate A 4.300 F9 6.810 Hill 3 others 1.3-bitsopropylenzane 4.500 F1,F2 49.15 Hill 3 others 1.4-bitsic2 (28-methyl-2-propanyl)berozene 4.500 F1,F2 NA NA NA others 1.3-bitsopropylenzane 0.600 F1,F2 NA NA 3 others	antioxidant	NDPHA / Nitrosodiphenylamine	3.130	F1,F2	42.65	Hill	7.84
antioxidant BHA / 3-Teri-butyl-4-hydroxyaniso (2-teri-Butyl-4-methoxypheno) 3.200 P9 0.139 pathway 2 intermediate Aminocaproic acid -2.950 FI,F2 inactive potency 3 intermediate Banzophenone 3.180 F9 0.400 pathway 6 intermediate Benzophenone 3.180 F9 0.400 pathway 6 UV absorber Tinuvin 1130 4.700 F2 NA NA NA UV absorber Octyl methoxycinnamate 5.300 F9 6.810 Hill 4 others 1.3-50isopropylhonzene 4.500 F1,F2 inactive constant 0 others 0.4bit2(2-methyl-2-proparyl)proxyl-2-propanylbenzene 4.500 F1,F2 NA NA NA others 0.4bit2(2-methyl-2-proparyl)proxyl-2-propanylbenzene 4.500 F1,F2 NA NA 3 others 1.4bit3(2-methyl-2-proparylproxyl-2-propanylbenzene 1.600 F1,F2 NA NA 3 </td <td>antioxidant</td> <td>Irgafos 168 (Antioxidant 168)</td> <td>15.500</td> <td>F9</td> <td>inactive</td> <td>potency</td> <td>NA</td>	antioxidant	Irgafos 168 (Antioxidant 168)	15.500	F9	inactive	potency	NA
intermediate4.000FINANANANAintermediateAminocopric acid-2,550FI,F2inactivepotencyIintermediate3.5,5-Trinethylyclohesenone (isophorone)1.700F2inactiveconstantIintermediateAnthraquinone3.390F91.2050Gain-loss2UV absorberPadimate A4.300F9inactiveconstant5UV absorberOctyl metonycinnamate2.300F96.810Hill3others1,3-Diisoproylbenzene4.500F1,F249.15Hill3others1,4-Bi2c1(2:methyl-2-propanyl)benzene4.500F1,F2NANANA3others1,4-Bi2c1(2:methyl-2-propanyl)benzene0.600F1,F2NANANA2others1,4-Bi2c1(2:methyl-2-propanyl)benzene0.600F1,F2NANANA2others1,4-Bi2c1(2:methyl-2-propanyl)benzene0.600F1,F2NANA2others1,4-Bi2c1(2:methyl-2-propanyl)benzene0.600F1,F2NANA9others1,4-Bi2c1(2:methyl-2-propanyl)benzene0.600F1,F2NANA9others0,4-Diperidine1.300F1,F2NANA9others0,2-Diperidine1.300F1,F2NANA9others1,1-Carbonylbsiperdine0.840F1,F2NANA0others1,1-Carbonylbsiperdine	antioxidant	BHA / 3-Tert-butyl-4-hydroxyanisole (2-tert-Butyl-4-methoxyphenol)	3.200	F9	0.0139	pathway	2.69
intermediateAninocaprois acid-2.98FI,P2inactivepotency3.7intermediate3.55. Tinethylyclobexenone (Isophorone)1.700F2inactiveconstant1.7intermediateAnthraquinone3.180F90.040pathway6UV absorberTinuvin 11304.700F2NANA1.1UV absorberPadimate A4.700F2NANANA1.1UV absorberOctyl methoxycinamate5.300F96.810Hill3.3others1.3-biogoropylbenzene4.500F1,F29.1NANANANothers1.3-biogoropylbenzene4.500F1,F2Inactiveconstant0.0others2.4Fgtenoic acid0.600F1,F2NANANA3othersCaprolactam cyclic dimer0.800F1,F2NANANA2othersCaprolactam cyclic dimer1.300F1,F2NANANA3othersNew/PEA1.300F1,F2NANANA3othersPhenylacrylic acid (Cinnamic acid)1.300F1,F2NANANA3others1.1-Carbonylibspiperdine1.400F2NANA10others1.1-Carbonylibspiperdine1.700F1,F2NANA10others1.1-Carbonylibspiperdine1.700F2NANA10others1.1-Carbonylibspiperdine <td< td=""><td>intermediate</td><td>4-tert-Butylcyclohexyl acrylate</td><td>4.000</td><td>F1</td><td>NA</td><td>NA</td><td>NA</td></td<>	intermediate	4-tert-Butylcyclohexyl acrylate	4.000	F1	NA	NA	NA
intermediate3,5,5-Tramethyleyclobexenone (Isophorone)1,700F2inactiveconstant1,700intermediateAnthraquinone3,180F91,20.50Gain-loss2UV aboorberTrauvin 1304,700F2NANANA1UV aboorberPadimate A4,300F9inactiveconstant55UV aboorberOctyl methoxycinnamate5,300F96,810Hill4others1,3-Disoproylbenzene4,500F1,F2Hill3others1,4-Bis(2 (2-methyl-2-propanyl)benzene4,500F1,F2,F9NANANAothers2-Heptenoic acid2,100F1NANANA9others3-Aminoacetophenone0,600F1,F2inactivepotency6othersCognolactam cyclic dimer0,600F1,F2NANANA9othersN-Me-DMPEA1,300F1,F2NANA9othersN-Me-DMPEA1,300F1,F2NANA3othersPiepridine0,400F2NANA3others1,4-Aitophylbispiperdine1,400F2NANA10others1,4-Aitophylbispiperdine1,400F2NANA10others1,4-Aitophylbispiperdine1,400F2NANA10others1,4-Aitophylbispiperdine5,000F2NANA10others1,	intermediate	Aminocaproic acid	-2.950	F1,F2	inactive	potency	37.61
Intermediate intermediate3.180P90.040pathwaybIntermediate AnthraquinoneAnthraquinone3.390F912.050Gain-loss2UV absorberPrinuvin 11304.700F2NANANA1UV absorberOctyl methoxycinnamate5.300F96.810Hill3others1.2-bisopropylbenzene4.500F1,F2P1NANANothers1.4-Bis(2-(2-methyl-2-propanyl)penxyl-2-propanyl)benzene4.500F1,F2NANANA3others3-Antinoacetophenone0.830F1,F2NANANA2othersCapolactam cyclic dimer0.860F1,F2NANANA2othersCapolactam cyclic dimer1.300F1,F2NANANA3othersOnumaric acid1.300F1,F2NANANA3othersNehoylic piperdine1.300F1,F2NANANA3othersNotachylic piperdine1.700F1P2NANA0others1_1-Carbonylispiperdine1.700F2NANA00others1_1-Carbonylispiperdine2.900F2NANA00others1_1-Carbonylispiperdine3.900F2NANA00others1_1-Carbonylispiperdine2.900F2NANA00others1_1-Carbo	intermediate	3,5,5-Trimethylcyclohexenone (Isophorone)	1.700	F2	inactive	constant	120.12
Intermediate Anthraquinone 3.39 F9 12.050 Gan-loss 2 UV absorber Tinuvin 130 4.700 F2 NA NA 1 UV absorber Padimate A 4.300 F9 inactive constant 1 UV absorber Orden techoxycinnamate 5.300 F9 6.810 Hill 4 others 1.3-Bifospropylbenzene 4.800 F1,F2 inactive constant 0 others 3-Heptenoic acid 2.100 F1 NA NA NA 9 others 3-Aminoacetophenone 0.830 F1,F2 NA NA 9 others Couraric acid 1.790 F1,F2 NA NA 9 others Phyeridine 0.800 F1 NA NA 9 others 1.4000 F2 NA NA 10 10 others 1.411/Carbonylbispiperdine 1.000 F2 NA NA 10 </td <td>intermediate</td> <td>Benzophenone</td> <td>3.180</td> <td>F9</td> <td>0.040</td> <td>pathway</td> <td>6.72</td>	intermediate	Benzophenone	3.180	F9	0.040	pathway	6.72
UV absorber Padmate A 4.300 F2 NA So obters 2.100 fr.122 NA NA NA NA So obters 1.14'Carbonylbispiperdine 1.400 DA NA NA NA	intermediate	Anthraquinone	3.390	F9	12.050	Gain-loss	2.85
UV absorberPadimate A4.300F96.810Hill4 5UV absorberOrtyl methoxyrinnamate5.300F96.810Hill3others1.3-Diisoproylbenzene4.500F1,F249.15Hill3others1.4-Bis(2-l(2-methyl-2-propanyl)peroxyl-2-propanyl)benzene4.500F1,F2inactiveconstantNothers3-Minoacetophenone0.830F1,F2Inactivepotency6.6othersCaprolactam cyclic dimer0.600F1,F2NANA20othersComaric acid1.700F1,F2NANA29othersComaric acid1.300F1,F2NANA29othersPhenylacrylic acid (Cinnamic acid)2.100F1,F2NANA9othersPhenylacrylic acid (Cinnamic acid)2.100F1,F2NANA8others1.1°Carbonylbispiperdine1.400F2NANA8others1.4°mico-2-naphthol1.700F2NANA6others1.4°mico-2-naphthol5.000F2,F9NANA0others1.4°mico-2-naphthol5.000F2NANA0others1.4°mico-2-naphthol5.000F2NANA0othersNonaethyleng glycolGarylace5.000F2NANA0othersNonaethyleng glycolGarylace3.300F6very weakNA0 <t< td=""><td>UV absorber</td><td>Tinuvin 1130</td><td>4.700</td><td>F2</td><td>NA</td><td>NA</td><td>1.17</td></t<>	UV absorber	Tinuvin 1130	4.700	F2	NA	NA	1.17
UV absorberDCP interboxycinnamate5.300F96.810Hill4others2.N300 ther2.1800FI,P249.15Hill3others1.4.bit2(12-methyl-2-propanyl)benzene4.500F1,P29.01NANANothers2.Heptenoic acid2.100F1NANA3others3-Aminoacetophenone0.600F1,P2NANA2othersCapotactam cyclic dimer0.600F1,P2NANA9othersCounaric acid1.300F1,P2NANA9othersOuters0.600F1,P2NANA9othersPhenylacrylic acid (Cinnamic acid)2.130F1,P2NANA8others1.1/-Carbonylbispiperline1.400F2NANA8others1.1/-Carbonylbispiperline1.400F2NANA6others1.1/-Carbonylbispiperline5.000F2NANA0others3.11 - 4.Cyano-1.2,3.4-tetrahydronaphyl)propanenitrile2.300F2NANA0othersNonaethylene glycolJasse3.300F2NANA0othersPD/ Diphenyll2,4.6-trimethylbenzoylphine oxide5.000F2NANA0othersThrborylongene triacrylate2.200F66.75Gain-lossNothersThrborylater trimethylopropane triacrylate2.200F66.75Gain-loss </td <td>UV absorber</td> <td>Padimate A</td> <td>4.300</td> <td>F9</td> <td>inactive</td> <td>constant</td> <td>5.19</td>	UV absorber	Padimate A	4.300	F9	inactive	constant	5.19
Outers2-Augnitypamine2.200F1, F249.15F1, fm5others1,4-Bis(2-{(2-methyl-2-propanyl)peroxyl-2-propanyl)benzene4.500F1, F2, F9NANANANAothers2-Heptenoic acid2100F1NANANA3others3-Aminoacetophenone0.830F1, F2inactivepotency6othersCaprolactam cyclic dimer0.600F1, F2NANA9othersCounaric acid1.790F1, F2NANA9othersPhenylacrylic acid (Cinnamic acid)2.130F1, F2NANA9othersPhenylacrylic acid (Cinnamic acid)1.300F1, F2NANA8others1,4'Carbonylbispiperdine0.840F1 F228.83potency1others1,4'Carbonylbispiperdine1.700F2NANA8others1,4'Carbonylbispiperdine1.700F2NANA0others3.11 - 4'Cyano-1,2,3'A tetrahydronaphyl)]propanenitrile2.400F2Inactivepotency5othersBBOT / 2,5-bit/S tert-Buryl-2 benzoxazolylbihophine oxide5.000F2Inactivepotency7othersThip/expleme3.300F6very weakpotency7othersThip/onylanel/penzylane3.380F6very weakpotency7othersBBOT / 2,5-bit/S tert-Buryl-2,6-crimethylbencylphonyline4.300F6inactive	UV absorber	Octyl methoxycinnamate	5.300	F9 E1 E2	6.810	Hill	4.41
Outers1,4-Bit SQL (2) methyl-2-propanyl)peroxyl-2-propanyl)benzene4.500F1,F2InactiveConstant0others2-Heptenoic acid2.100F1NANANASothers3-Aminoacetophenone0.600F1,F2NANANA2othersCaprolactam cyclic dimer0.600F1,F2NANANA2othersCoumaric acid1.700F1,F2NANANA3othersOutersPhenylacrylic acid (Cinnamic acid)2.130F1,F2NANA8othersPhenylacrylic acid (Cinnamic acid)2.130F1,F2NANA8othersPhenylacrylic acid (Cinnamic acid)2.130F1,F2NANA8others1,4-Gabonylbispiperdine1.400F2NANA8others1,1-4-Cabonylbispiperdine1.400F2NANA0others3.11 - 4-Cyano-1,2,3.4+tetrahydronapthyl)]propanenitrile2.400F2NANA0othersBBOT / 2,5-bis(5+ter.Burgl-2-benzoxazolylbhophene8.000F2Inactivepotency0othersTirlorommethyl phenylsulfone3.900F2NANA0othersTirlorommethyl phenyl sulfone3.900F2NANA0othersTheodo // Triforop/ee glycol) diacrylate2.200F2inactivepotencyNothersBenzil3.300F6very weakpotency<	others	2-Naphthylamine	2.280	F1,F2	49.15	HIII	3./3
Outers1,4-bik 2-(traineth)-2-(pr)aphy)(per)oxy)-2-propany)(per)ox)NANANA3othersCommaric acid1.790F1,F2NANANA9othersN-Me-DMPEA1.300F1,F2inactiveconstant2othersPiperidine0.840F1 F228.83potency11others1,4/Carbony)bispiperdine1.400F2NANA8others1,4/Carbony)bispiperdine1.700F2NANA0others2,2-(Tridecy)azanediy)diethanol1.700F2NANA0others3(1 - 4-Cyano) 1,2,3-4-tertahydronapthyl)]propanenitrile2.400F2inactivepotency0othersBBOT / 2,5-bis(5-tert-Butyl-2-benzoxazolyl)thiophene8.000F2inactivepotency0othersThirdomomethyl phenyl sulfore3.300F2NANA0othersThirdomomethyl phenyl sulfore3.300F6very weakpotency7othersThirdomomethyl phenyl sulfore4.500F9inactiveconstantNothersBenzil3.380F6very weakpotency	others	1,3-Disopropyidelizene	4.500	F1,F2 E1 E2 E0	Macuve	Constant	0.84 NA
Outlers2-Indpending and 2-100P1PAPAPAPAothersGaprolactam cyclic dimer0.600F1,F2NANA20othersCoumaric acid1.790F1,F2NANA20othersN-Me-DMPEA1.300F1,F2NANA90othersPhenylacrylic acid (Cinnamic acid)2.130F1,F2NANA33othersPhenylacrylic acid (Cinnamic acid)2.130F1,F2Inactiveconstant22others1,1'Carbonylbispiperdine1.400F2NANA86others1,1'Carbonylbispiperdine1.700F2NANA66others1.2,3,4'tetrahydronapthyl)propanenitrile2.400F2NANA00othersS-bis(5-tert-Buryl-2-benzoxazolyl)thiophene8.000F2Inactivepotency00othersNonaethylene glycol-2.300F2Inactivepotency00othersTribromomethyl phenyl sulfone3.900F2NANA00othersTribromomethyl phenyl sulfone3.900F2InactiveconstantN1othersBenzil3.200F66.75Gain-JossN1othersBenzil3.800F60.00983pathway1.othersBenzilS.700F9InactiveconstantN3othersHexyl cinnamaldehyde4.500F9Inactiveconstant1.<	others	1,4-Bis(2-[(2-inethyl-2-propanyl)peroxy]-2-propanyl)penzene	4.300	F1,F2,F9 F1	NA	NA NA	NA 21 E1
OthersS-Aminoactopinetione0.830F1,F2Inactivepolency0othersCoumaric acid1.790F1,F2NANA9othersN-Me-DMPEA1.300F1,F2NANA3othersPhenylacrylic acid (Cinnamic acid)2.130F1,F2inactiveconstant2othersPiperidine0.840F1 F228.83potency11others1,1'Carbonylbispiperdine1.400F2NANA8others2,2-(Tridecylazanediyl)ditehanol5.000F2,F9NANA13others3-(1 - 4-Cyano-1,2,3,4-tetrahydronapthyl)propanenitrile2.400F2inactivepotency0.0othersBOT / 2,5-bit6/stert-Butyl-2-benzoxazolyl)thiophene8.000F2inactivepotency0.0othersNonaethylene glycol-2.300F2inactivepotency5.00othersTRPO / Diphenyl (2,4,6-trimethylbenzyl)phosphine oxide5.000F2inactiveconstantN0.0othersTRPGDA / Tri(propylene glycol) diacrylate2.200F66.75Gain-lossNN0.0othersHexyl cinnamaldehyde4.800F6inactiveconstantN0.0othersHexyl cinnamaldehyde5.400F6inactiveconstantN0.0othersTriftphene glycol bis(2-ethylhexanote)5.400F6inactiveconstant1.0othersTriethylene gly	others	2-Meinensetenbenene	2.100	F1 E1 E2	inactivo	NA	6 50
OthersCapitolation (vince infinite)0.000 F_1,F_2 NANA9othersN-Me-DMPEA1.300 F_1,F_2 NANA9othersPhenylacrylic acid (Cinnamic acid)2.130 F_1,F_2 inactiveconstant2othersPiperidine0.840 F_1F_2 28.83potency1others1,1'C-arbonylbispiperdine1.400 F_2 NANA8others1,1'C-arbonylbispiperdine1.700 F_2 NANA6others2,2'(Tridecylazanediyl)diethanol5.000 F_2 NANA0.0others3-[1 - 4-Cyano-1,2,3,4-tetrahydronapthyl)]propanenitrile2.400 F_2 NANA0.0others3-[1 - 4-Cyano-1,2,3,4-tetrahydronapthyl)]propanenitrile2.400 F_2 NANA0.0others3-[1 - 4-Cyano-1,2,3,4-tetrahydronapthyl)]propanenitrile2.400 F_2 NANA0.0othersBOD/ 2,5-bit5-tetr-Butyl-2-benzoxazolyl)thiophene8.000 F_2 NANA0.0othersTribromomethyl phenyl sulfone9.000 F_2 NANA0.0othersTRPGDA / Tri(propylene glycol) diacrylate2.200 F_2 inactiveconstantNAothersHexyl cinnamaldehyde4.800F6inactiveconstant3.3othersHexyl cinnamaldehyde4.800F6inactiveconstant3.3othersHexyl cinnamaldehyde5.700F9	others	Caprolactam cyclic dimer	0.600	F1,F2 F1 F2	MA	NA	260.32
OthersOrderFind <th< td=""><td>others</td><td>Coumaric acid</td><td>1 790</td><td>F1,F2 F1 F2</td><td>NA</td><td>NA</td><td>200.32 9.57</td></th<>	others	Coumaric acid	1 790	F1,F2 F1 F2	NA	NA	200.32 9.57
OthersPherylarrylic acid (Cinnamic acid)2.130F1,F2F1,F2F1,F2InactiveConstant2othersPiperidine0.840F1 F228.83potency1others1,1'Carbonylbispiperdine1.400F2NANA86others1,4'mino-2-naphthol1.700F2NANA66others2,2-(Tridecylazanediyl)diethanol5.000F2,F9NANA00others3-11 - 4-Cyano-1,2,3.4 +tetrahydronapthyl)]propanenitrile2.400F2NANA00others3-11 - 4-Cyano-1,2,3.4 +tetrahydronapthyl)]propanenitrile2.400F2NANA00others3-11 - 4-Cyano-1,2,3.4 +tetrahydronapthyl)]propanenitrile2.400F2NANA00othersNonaethylene glycol-2.300F2NANA00othersTIPO / Diphenyl(2,4.6-trimethylbenzoyl)phosphine oxide5.000F2NANA00othersTRPGDA / Tri(propylene glycol) diacrylate2.200F2NANA00othersBenzil3.380F6very weakpotency7othersHenzyl cinnamaldehyde4.800F6inactiveconstantNothersHenzyl cinnamaldehyde4.800F6inactiveconstant3.30othersTirethylene glycol bis(2-ethylhexanoate)5.400F6inactiveconstant3.30othersTirethylene glycol bis(2-ethylhexanoate)5.4	others	N-Me-DMPFA	1 300	F1 F2	NA	NA	31 21
othersPiperidineDetermine tendsDetermine tendsDetermine tendsothers1,1'-Carbonylbispiperdine1.400F2NANA8others1,4mino-2-naphthol1.700F2NANA8others2,2-(Tridecylazanediyl)diethanol5.000F2,PNANA1others3.[1 - 4.Cyano-1,2,3.4-tetrahydronapthyl)]propanenitrile2.400F2NANA0othersBBOT / 2,5-bit(5-tetr-Butyl-2-benzoazolyl)thiophene8.000F2inactivepotency0.othersBBOT / 2,5-bit(5-tetr-Butyl-2-benzoazolyl)thiophene8.000F2inactivepotency0.othersTPO / Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide5.000F2S6.29Hill0.othersTribronomethyl phenyl sulfone3.900F2NANA0.othersTribronomethyl phenyl sulfone3.380F6very weakpotency7.othersBenzil3.380F6very weakpotency7.othersHenxyl cinnamalehyde4.800F6inactiveconstantNothersTriethylene glycol biacrylate5.400F6inactiveconstant3.othersTriethylene glycol biacrylate5.400F6inactiveconstant3.othersTriethylene glycol biacrylate5.700F9inactiveconstant3.othersTriethylene glycol biacrylate5.700F9inactive </td <td>others</td> <td>Phenylacrylic acid (Cinnamic acid)</td> <td>2 1 30</td> <td>F1 F2</td> <td>inactive</td> <td>constant</td> <td>26.05</td>	others	Phenylacrylic acid (Cinnamic acid)	2 1 30	F1 F2	inactive	constant	26.05
others1,1'-Carbonylbispiperdine1,400F12NANA8others1,4'-Carbonylbispiperdine1,700F2NANANA6others2,2-(Tridecylazanediyl)diethanol5.000F2NANANA0others3,11-4-Cyano-1,2,3,4-tetrahydronapthyl)]propanenitrile2,400F2NANA0othersBBOT / 2,5-bis(5-tert-Butyl-2-benzoxazolyl)thiophene8.000F2inactivepotency5.000othersNonaethylene glycol-2.300F2inactivepotency5.000othersTribromomethyl phenyl sulfone3.900F2NANA0.00othersTRPGDA / Tri(propylene glycol) diacrylate2.200F2inactiveconstantNNothersBenzil3.380F6very weakpotency7.7othersBenzil3.380F6very weakpotency7.7othersHexyl cinnamaldehyde4.800F60.00983pathway1.7othersMyristamine oxide6.400F6inactiveconstant3.3othersTrichtylene glycol bis(2-ethylhexanoate)5.400F6inactiveconstant3.7othersN/-Ethylenebis(staramide)6.800F9inactiveconstant1.7othersN/-Sthylenebis(staramide)5.700F9inactiveconstant1.7othersN/-Sthylenebis(staramide)5.700F9inactive <t< td=""><td>others</td><td>Pineridine</td><td>0.840</td><td>F1 F2</td><td>28.83</td><td>potency</td><td>101 59</td></t<>	others	Pineridine	0.840	F1 F2	28.83	potency	101 59
others1-Amino-2-naphthol1.700F2NANANAothers2,2-(Tridecylazanediyl)diethanol5.000F2,F9NANANA1others3-[1 - 4-Cyano-1,2,3,4-tetrahydronapthyl)]propanenitrile2.400F2NANA0othersBBOT / 2,5-bis(5-tert-Butyl-2-benzoxazolyl)thiophene8.000F2inactivepotency0.othersNonaethylene glycol-2.300F2inactivepotency5.othersTPO / Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide5.000F256.29Hill0.othersTribromomethyl phenyl sulfone3.900F2NANA0.othersTRPGDA / Tri(propylene glycol) diacrylate2.200F2inactiveconstantNothersBenzil3.380F6very weakpotency7.othersEthoxylated trimethylolpropane triacrylate2.200F66.75Gain-lossNothersHexyl cinnamaldehyde4.800F6inactivepotencyNothersTriethylene glycol bis(2-ethylhexanoate)5.400F6inactiveconstant3.othersStearamide (Octadecanamide)6.800F9inactiveconstant1.othersStearamide (Octadecanamide)5.700F9inactivepotency0.othersN,N'Ethylenebis(stearamide)5.700F9inactivepotency0.othersEthylene azelate2.000 <td>others</td> <td>1.1'-Carbonylbispiperdine</td> <td>1.400</td> <td>F2</td> <td>NA</td> <td>NA</td> <td>81.94</td>	others	1.1'-Carbonylbispiperdine	1.400	F2	NA	NA	81.94
others2,2-(Tridecylazanediyl)diethanol5,000F2,F9NANA1others3-[1 - 4-Cyano-1,2,3,4-tetrahydronapthyl)]propanenitrile2.400F2NANA0othersBBOT / 2,5-bit(5-tert-Butyl-2-benzoxazolyl)thiophene8.000F2inactivepotency0othersNonaethylene glycol-2.300F2inactivepotency0othersTPO / Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide5.000F256.29Hill0othersTribronomethyl phenyl sulfone3.900F2NANA0othersTRPGDA / Tri(propylene glycol) diacrylate2.200F2inactiveconstantNothersBenzil3.380F6very weakpotency7.othersEthoxylated trimethylolpropane triacrylate2.200F66.75Gain-lossNothersMyristamine oxide6.400F6inactivepotencyNothersMyristamine oxide6.400F6inactiveconstant3.others2-Ethylhexyl benzoate4.500F9inactiveconstant1.othersStearamide (Octadecanamide)5.700F9inactivepotency1.othersN,N'-Ethylene bis(stearamide)5.700F9inactiveconstant1.othersN,N'-Ethylene bis(stearamide)5.700F9inactiveconstant1.othersBtrl-quinone methide (2,6-di-tert-butyl-4-methylene-2,5	others	1-Amino-2-naphthol	1.700	F2	NA	NA	6.23
others3-[1 - 4-Cyano-1,2,3,4-tetrahydronapthyl]]propanenitrile2.400F2NANA0othersBBOT / 2,5-bis(5-tert-Butyl-2-benzoxazolyl)thiophene8.000F2inactivepotency0othersNonaethylene glycol-2.300F2inactivepotency5othersTPO / Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide5.000F256.29Hill0.othersTRPGDA / Tri(propylene glycol) diacrylate2.200F2NANA0.othersBenzil3.380F6very weakpotency7.othersEthoxylated trimethylopropane triacrylate2.200F66.75Gain-lossNothersHexyl cinnamaldehyde4.800F6inactivepotencyNothersMyristamine oxide6.400F6inactivepotencyNothersTriethylene glycol bis(2-ethylhexanoate)5.400F6inactiveconstant3.othersStearamide (Octadecanamide)6.800F9inactiveconstant1.othersRicinolic acid (Ricinoleic acid)5.700F9inactivepotency1.othersEthylene bis(stearamide)15.700F9NANA88othersEthylene azelate2.000F9NANA88othersEthylene bis(stearamide)15.700F9NANA88othersBHT-quinone methide (2,6-di-tert-butyl-4-methylene-2,5- cyclohexandienone) </td <td>others</td> <td>2.2-(Tridecvlazanedivl)diethanol</td> <td>5.000</td> <td>F2.F9</td> <td>NA</td> <td>NA</td> <td>15.78</td>	others	2.2-(Tridecvlazanedivl)diethanol	5.000	F2.F9	NA	NA	15.78
othersBBOT / 2,5-bis(5-tert-Butyl-2-benzoxazolyl)thiophene8.000F2inactivepotency0othersNonaethylene glycol-2.300F2inactivepotency5othersTPO / Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide5.000F256.29Hill0othersTribromomethyl phenyl sulfone3.900F2NANA0.othersTRPGDA / Tri(propylene glycol) diacrylate2.200F2inactiveconstantNothersBenzil3.380F6very weakpotency7.othersEthoxylated trimethylolpropane triacrylate2.200F66.75Gain-lossNothersHexyl cinnamaldehyde4.800F6inactivepotencyNothersMyristamine oxide6.400F6inactiveconstant3.othersTriethylene glycol bis(2-ethylhexanoate)5.400F6inactiveconstant3.othersStearamide (Octadecanamide)6.800F9inactiveconstant1.othersRicinolic acid (Ricinoleic acid)5.700F9inactivepotency0.othersEthylenebis(stearamide)15.700F9NANA88othersBHT-quinone methide (2,6-di-tert-butyl-4-methylene-2,5- cyclohexandienone)4.600F9NANA0.others3,5-di-tert-butyl-4-methylene-2,5- cyclohexandienone)4.600F9NANA0.	others	3-[1 – 4-Cyano-1.2.3.4-tetrahydronapthyl)]propanenitrile	2.400	F2	NA	NA	0.51
othersNonaethylene glycol-2.300F2inactivepotency5othersTPO / Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide5.000F256.29Hill0othersTribromomethyl phenyl sulfone3.900F2NANA0othersTRPGDA / Tri(propylene glycol) diacrylate2.200F2inactiveconstantNothersBenzil3.380F6very weakpotency7.othersEthoxylated trimethylolpropane triacrylate2.200F66.75Gain-lossNothersHexyl cinnamaldehyde4.800F60.00983pathway1.othersMyristamine oxide6.400F6inactiveconstant3.othersTribylene glycol bis(2-ethylhexanoate)5.400F6inactiveconstant3.othersStearamide (Octadecanamide)6.800F9inactiveconstant1.othersRicinolic acid (Ricinoleic acid)5.700F9inactiveconstant1.othersRichylene glycol-ethyl-4-methylene-2,5- cyclohexandienone)2.000F9NANA88othersHHT-quinone methide (2,6-di-tert-butyl-4-methylene-2,5- cyclohexandienone)4.600F9NANA0.others4-Phenylbenzophenone (4-Benzoylbiphenyl)4.900F9NANA0.others3,5-di-tert-butyl-4-hydroxyacetophenone4.600F9NANA0.	others	BBOT / 2,5-bis(5-tert-Butyl-2-benzoxazolyl)thiophene	8.000	F2	inactive	potency	0.0957
othersTPO / Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide5.000F256.29Hill0othersTribromomethyl phenyl sulfone3.900F2NANA00othersTRPGDA / Tri(propylene glycol) diacrylate2.200F2inactiveconstantNNothersBenzil3.380F6very weakpotency7.othersEthoxylated trimethylolpropane triacrylate2.200F66.75Gain-lossNNothersHexyl cinnamaldehyde4.800F60.00983pathway1.othersMyristamine oxide6.400F6inactivepotencyNothersTriehylene glycol bis(2-ethylhexanoate)5.400F6inactiveconstant3.3others2-Ethylhexyl benzoate4.500F945.500Hill2.othersStearamide (Octadecanamide)6.800F9inactiveconstant1.othersN/-Ethylenebis(stearamide)5.700F9inactivepotency0.othersN/-Ethylenebis(stearamide)15.700F9inactivepotency0.othersBHT-quinone methide (2,6-di-tert-butyl-4-methylene-2,5- cyclohexandienone)F9NANA82others3,5-di-tert-butyl-4-hydroxyacetophenone4.600F9NANA0.others3,5-di-tert-butyl-4-hydroxyacetophenone4.600F9NANA0.	others	Nonaethylene glycol	-2.300	F2	inactive	potency	546.82
othersTribromomethyl phenyl sulfone3.900F2NANA0othersTRPGDA / Tri(propylene glycol) diacrylate2.200F2inactiveconstantNothersBenzil3.380F6very weakpotency7.othersEthoxylated trimethylolpropane triacrylate2.200F66.75Gain-lossNothersHexyl cinnamaldehyde4.800F60.00983pathway1.othersMyristamine oxide6.400F6inactivepotencyNothersTriethylene glycol bis(2-ethylhexanoate)5.400F6inactiveconstant3.others2-Ethylhexyl benzoate4.500F945.500Hill2.othersStearamide (Octadecanamide)6.800F9inactiveconstant1.othersN/-Ethylenebis(stearamide)5.700F9inactiveconstant1.othersN/-Ethylenebis(stearamide)15.700F9inactiveconstant1.othersBHT-quinone methide (2,6-di-tert-butyl-4-methylene-2,5- cyclohexandienone)F9NANANA0.others4-Phenylbenzophenone (4-Benzoylbiphenyl)4.900F9NANA0.others3,5-di-tert-butyl-4-hydroxyacetophenone4.600F9NANA0.	others	TPO / Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide	5.000	F2	56.29	Hill	0.036
othersTRPGDA / Tri(propylene glycol) diacrylate2.200F2inactiveconstantNothersBenzil3.380F6very weakpotency7othersEthoxylated trimethylolpropane triacrylate2.200F66.75Gain-lossNothersHexyl cinnamaldehyde4.800F60.00983pathway1.othersMyristamine oxide6.400F6inactivepotencyNothersTriethylene glycol bis(2-ethylhexanoate)5.400F6inactiveconstant3.others2-Ethylhexyl benzoate4.500F945.500Hill2.othersStearamide (Octadecanamide)6.800F9inactiveconstant1.othersRicinolic acid (Ricinoleic acid)5.700F9inactiveconstant1.othersN/Y-Ethylenebis(stearamide)15.700F9inactivepotency0.othersEthylene azelate2.000F9NANA82othersBHT-quinone methide (2,6-di-tert-butyl-4-methylene-2,5- cyclohexandienone)4.900F9NANA0.others4-Phenylbenzophenone (4-Benzoylbiphenyl)4.900F9NANA0.others3,5-di-tert-butyl-4-hydroxyacetophenone4.600F9NANA0.	others	Tribromomethyl phenyl sulfone	3.900	F2	NA	NA	0.36
othersBenzil3.380F6very weakpotency7othersEthoxylated trimethylolpropane triacrylate2.200F66.75Gain-lossNothersHexyl cinnamaldehyde4.800F60.00983pathway1.othersMyristamine oxide6.400F6inactivepotencyNothersTriethylene glycol bis(2-ethylhexanoate)5.400F6inactiveconstant3.others2-Ethylhexyl benzoate4.500F945.500Hill2.othersStearamide (Octadecanamide)6.800F9inactivepotency1.othersRicinolic acid (Ricinoleic acid)5.700F9inactiveconstant1.othersN.N'-Ethylenebis(stearamide)15.700F9inactivepotency0.othersEthylene azelate2.000F9NANA80othersBHT-quinone methide (2,6-di-tert-butyl-4-methylene-2,5- cyclokexandienone)4.900F9weak activepotency0.others3,5-di-tert-butyl-4-hydroxyacetophenone4.600F9NANA0.	others	TRPGDA / Tri(propylene glycol) diacrylate	2.200	F2	inactive	constant	NA
othersEthoxylated trimethylolpropane triacrylate2.200F66.75Gain-JossNothersHexyl cinnamaldehyde4.800F60.00983pathway1othersMyristamine oxide6.400F6inactivepotencyNothersTriethylen glycol bis(2-ethylhexanoate)5.400F6inactiveconstant3.3others2-Ethylhexyl benzoate4.500F945.500Hill2othersStearamide (Octadecanamide)6.800F9inactivepotency1.3othersRicinolic acid (Ricinoleic acid)5.700F9inactivepotency0.3othersN.N'-Ethylenebis(stearamide)15.700F9inactivepotency0.3othersEthylene azelate2.000F9NANA83othersBHT-quinone methide (2,6-di-tert-butyl-4-methylene-2,5- cyclohexandienone)4.900F9weak activepotency0.3others3,5-di-tert-butyl-4-hydroxyacetophenone4.600F9NANA0.3	others	Benzil	3.380	F6	very weak	potency	7.780
othersHexyl cinnamaldehyde4.800F60.00983pathway1.othersMyristamine oxide6.400F6inactivepotencyNothersTriethylene glycol bis(2-ethylhexanoate)5.400F6inactiveconstant3.others2-Ethylhexyl benzoate4.500F945.500Hill2.othersStearamide (Octadecanamide)6.800F9inactivepotency1.othersRicinolic acid (Ricinoleic acid)5.700F9inactiveconstant1.othersRicholeic acid)5.700F9inactivepotency0.othersEthylene bis(stearamide)15.700F9inactivepotency0.othersEthylene azelate2.000F9NANA88othersBHT-quinone methide (2,6-di-tert-butyl-4-methylene-2,5- cyclohexandienone)4.600F9NANA0.others3,5-di-tert-butyl-4-hydroxyacetophenone4.600F9NANA0.	others	Ethoxylated trimethylolpropane triacrylate	2.200	F6	6.75	Gain-loss	NA
othersMyristamine oxide6.400F6inactivepotencyNothersTriethylene glycol bis(2-ethylhexanoate)5.400F6inactiveconstant3others2-Ethylhexyl benzoate4.500F945.500Hill2othersStearamide (Octadecanamide)6.800F9inactivepotency1othersRicinolic acid (Ricinoleic acid)5.700F9inactiveconstant1othersN.N'-Ethylenebis(stearamide)15.700F9inactivepotency0othersBthylene azelate2.000F9NANA82othersBHT-quinone methide (2,6-di-tert-butyl-4-methylene-2,5- cyclohexandienone)4.600F9NANA0others4-Phenylbenzophenone (4-Benzoylbiphenyl)4.900F9weak activepotency0others3,5-di-tert-butyl-4-hydroxyacetophenone4.600F9NANA0	others	Hexyl cinnamaldehyde	4.800	F6	0.00983	pathway	1.290
othersTriethylene glycol bis(2-ethylhexanoate)5.400F6inactiveconstant3others2-Ethylhexyl benzoate4.500F945.500Hill2.othersStearamide (Octadecanamide)6.800F9inactivepotency1.othersRicinolic acid (Ricinoleic acid)5.700F9inactiveconstant1.othersN,N'-Ethylenebis(stearamide)15.700F9inactivepotency0.othersEthylene azelate2.000F9NANA82othersBHT-quinone methide (2,6-di-tert-butyl-4-methylene-2,5- cyclohexandienone)4.600F9NANA0.others4-Phenylbenzophenone (4-Benzoylbiphenyl)4.900F9weak activepotency0.others3,5-di-tert-butyl-4-hydroxyacetophenone4.600F9NANA0.	others	Myristamine oxide	6.400	F6	inactive	potency	NA
others2-Ethylhexyl benzoate4.500F945.500Hill2othersStearamide (Octadecanamide)6.800F9inactivepotency1.othersRicinolic acid (Ricinoleic acid)5.700F9inactiveconstant1.othersN/N-Ethylenebis(stearamide)15.700F9inactivepotency0.othersN/N-Ethylenebis(stearamide)15.700F9inactivepotency0.othersBHT-quinone methide (2,6-di-tert-butyl-4-methylene-2,5- cyclohexandienone)4.600F9NANA0.others4-Phenylbenzophenone (4-Benzoylbiphenyl)4.900F9weak activepotency0.others3,5-di-tert-butyl-4-hydroxyacetophenone4.600F9NANA0.	others	Triethylene glycol bis(2-ethylhexanoate)	5.400	F6	inactive	constant	3.210
othersStearamide (Octadecanamide)6.800F9inactivepotency1othersRicinolic acid (Ricinoleic acid)5.700F9inactiveconstant1othersN,N'-Ethylenebis(stearamide)15.700F9inactivepotency00othersEthylene azelate2.000F9NANA88othersBHT-quinone methide (2,6-di-tert-butyl-4-methylene-2,5- cyclohexandienone)4.600F9NANA80others4-Phenylbenzophenone (4-Benzoylbiphenyl)4.900F9weak activepotency00others3,5-di-tert-butyl-4-hydroxyacetophenone4.600F9NANA00	others	2-Ethylhexyl benzoate	4.500	F9	45.500	Hill	2.73
othersRicinolic acid (Ricinoleic acid)5.700F9inactiveconstant1othersN,N'-Ethylenebis(stearamide)15.700F9inactivepotency0.othersEthylene azelate2.000F9NANA83othersBHT-quinone methide (2,6-di-tert-butyl-4-methylene-2,5- cyclohexandienone)4.600F9NANA0.others4-Phenylbenzophenone (4-Benzoylbiphenyl)4.900F9weak activepotency0.others3,5-di-tert-butyl-4-hydroxyacetophenone4.600F9NANA0.	others	Stearamide (Octadecanamide)	6.800	F9	inactive	potency	1.030
othersN,N'-Ethylenebis(stearamide)15.700F9inactivepotency0othersEthylene azelate2.000F9NANA82othersBHT-quinone methide (2,6-di-tert-butyl-4-methylene-2,5- cyclohexandienone)4.600F9NANA0.others4-Phenylbenzophenone (4-Benzoylbiphenyl)4.900F9weak activepotency0.others3,5-di-tert-butyl-4-hydroxyacetophenone4.600F9NANA0.	others	Ricinolic acid (Ricinoleic acid)	5.700	F9	inactive	constant	1.850
othersEthylene azelate2.000F9NANA8othersBHT-quinone methide (2,6-di-tert-butyl-4-methylene-2,5- cyclohexandienone)4.600F9NANA0.others4-Phenylbenzophenone (4-Benzoylbiphenyl)4.900F9weak activepotency0.others3,5-di-tert-butyl-4-hydroxyacetophenone4.600F9NANA0.	others	N,N'-Ethylenebis(stearamide)	15.700	F9	inactive	potency	0.760
othersBHT-quinone methide (2,6-di-tert-butyl-4-methylene-2,5- cyclohexandienone)4.600F9NANA0.others4-Phenylbenzophenone (4-Benzoylbiphenyl)4.900F9weak activepotency0.others3,5-di-tert-butyl-4-hydroxyacetophenone4.600F9NANA0.	others	Ethylene azelate	2.000	F9	NA	NA	82.820
others4-Phenylbenzophenone (4-Benzoylbiphenyl)4.900F9weak activepotency0.others3,5-di-tert-butyl-4-hydroxyacetophenone4.600F9NANA0.	others	BHT-quinone methide (2,6-di-tert-butyl-4-methylene-2,5- cyclohexandienone)	4.600	F9	NA	NA	0.820
others 3,5-di-tert-butyl-4-hydroxyacetophenone 4.600 F9 NA NA 0.	others	4-Phenylbenzophenone (4-Benzovlbiphenyl)	4.900	F9	weak active	potency	0.890
	others	3,5-di-tert-butyl-4-hydroxyacetophenone	4.600	F9	NA	NA	0.730
others 1,3:2,4-bis(3,4-dimethylbenzylidene)sorbitol 2.800 F9 inactive Gain-loss N	others	1,3:2,4-bis(3,4-dimethylbenzylidene)sorbitol	2.800	F9	inactive	Gain-loss	NA

elicit greater responses *in vivo* relative to *in vitro* activities, such as the case for the F6 fraction (Fig. 1). Previous studies have reported similar phenomenon. Mixtures of phenol ethoxylates with both diuron and bifenthrin, showed higher *vtg* mRNA expression in male fathead minnow compared to treatments with the individual compounds (Crago et al., 2015). This may be due to enhanced biotransformation of other non-estrogenic compounds to active metabolites. For example, alkylphenol pretreatment induced the demethylation of the herbicide, and diuron formed the metabolite 3,4-dichlorophenyl-*N*-methylurea, which had a stronger estrogenic signal than diuron in juvenile male tilapia (Felicio et al., 2016).

Alternatively, bioassay markers may have different sensitivities to the direct activation of the estrogen receptors, especially with the presence of other compounds. For example, several compounds have been shown to enhance endogenous estradiol levels (Crago et al., 2015; Felicio et al., 2016). And, in some cases compounds (i.e., 17a-ethynylestradiol (EE2)) have been shown to have higher in vivo (zebrafish VTG protein expression) estrogenic activity compared to in vitro (MVLN assay) responses (Van den Belt et al., 2004). Thus, in vivo estrogenic assays may be more sensitive than in vitro tests, due to metabolism and other non-ER targets that can enhance estrogenicity besides direct activation of ER (Van den Belt et al., 2004). Although in vitro assays can be applied as screening assays for qualitative assessment of estrogenicity because of high throughput logistics, the in vivo assays may be needed for an accurate hazard assessment for wildlife. It is noteworthy that the sum of biological responses from the whole extract was less than individual fractions. This phenomenon can be due to the presence of antagonistic compounds in the complicated whole extracts (Šauer et al., 2018; Hashmi et al., 2020), or due to the lowered bioavailaibility of chemicals in the whole extract with the presence of plastic oligomers (Chen et al., 2019b).

There are various sources of estrogen-like chemicals in the plastic bags. On the one hand, different kinds of additives are often added in the manufacturing of polyethylene shopping bags. On the other hand, the plastic bag used in this study contains at least 20 % of recycled polyethylene plastic as marked on the bags, and the plastic recycling process can bring in many other pollutants. First, halogens can accumulate in the cement kiln system of plastic waste recycling processes (Hahladakis et al., 2018; UNEP, 2015). We did find many chemicals with Cl and Br atoms in the NTS. Second, recycled plastics are usually transported over long distances, during which many pollutants can also adhere to plastics (PlasticsEurope, 2010). Third, it has been reported that due to multiple extrusion steps during the waste plastic recycling, multiple contaminants can be introduced into the recycled plastic products (Peres et al., 2016).

3.2. Acute and sub-acute toxicity of plastic leachate (sub)fractions to medaka

Lethality was measured in medaka embryos 4 dpf following exposure and indicated there were no significant differences between fraction treatments and negative/solvent controls (Fig. 2A). Similarly, cytotoxicity was not observed in the ER bioassays for either whole extracts or fractions after 24 h exposure.

In contrast, heart rate (5 dpf) decreased significantly from 60 ± 5 beats/min to 51 ± 4 beats/min when comparing the whole plastic extracts with control (p < 0.05) (Fig. 2B). Besides, significant reduction of hatching rate (10 dpf) was observed following exposure, with the whole extract, F1 fraction, and F2 fraction relative to control, respectively (Fig. 2C). Japanese medaka embryos failed to hatch after the whole extract and the F1 fraction exposure. There were 4273 entities in the whole extract, with 64 % of the compounds concentrated in the first two fractions, (776 entities in the F1 fraction, and 1071 entities in the F2 fraction) (Fig. 2D).

In the F1 and F2 fractions, although few chemicals possessed estrogenic activity, some might have had toxic effects in aquatic organisms. Here we used the LC_{50} values for *Daphnia magna* obtained from the T.E.S.T. database (Martin, 2016), with which data to reflect the acute toxicity of the detected compounds (Martin, 2016). For example, several compounds had 48 h LC_{50} values less than 1 mg/L (2,4,6-trimethylbenzoylphenylphosphinic acid ethyl ester, isopropyl diphenylamine, 1,3-diisopropylbenzene, 3-[1-4-Cyano-1,2,3,4-tetrahydronapthyl] propanenitrile, BBOT, TPO, and tribromomethyl phenyl sulfone) were detected, deserves our further attention (Table 1).

Also, several other novel compounds were identified in the first two fractions, including chemical initiators (2,4-diethylthioxanthone (DETX) and 2-chlorthioxanthone), colouring pigments (toluidine blue and 2,4-dinitrophenol), polymer synthesis intermediates (4-*tert*-butylk cyclohexyl acrylate, aminocaproic acid, and NDPHA (nitrosodiphenylamine)), antioxidants (2-naphthylamine, 2,5-DBQ (2,5-Di-*tert*-butylbenzoquinone), isopropyl diphenylamine), and the UV-



Fig. 2. Acute and sub-acute toxicity endpoints for Japanese medaka after plastic leachate exposure and chemical entities in the leachate. (A) lethality of medaka embryo on 4 dpf; (B) heartbeat rate of medaka embryo on 5 dpf; (C) medaka larvae hatching rate on 10 dpf; (D) chemical entities detected by non-target screening in different fractions and subfractions. ctrl: negative control; SC: solvent control; whole: the whole extract of the plastic leachate. F1-10: fractions 1-10; SF: sub-fractions.

absorbent, tinuvin 1130. However, these compounds had relatively lower acute toxicity based on LC50 values. Antioxidants are usually embedded into plastics to inhibit polymer oxidative degradation when exposed to ultraviolet (UV) light (Bhunia et al., 2013; Hahladakis et al., 2018). Soluble azocolorants, which can provide a variety of colours for plastic packaging (Groh et al., 2019). The two colorants detected in the study were blue (toluidine blue) and yellow (2,4-dinitrophenol), which was consistent with the green appearance on the shopping bags (Fig. S2). Catalyst residues, such as initiators, may remain on the plastic after manufacturing even though most of the initiators can be neutralized by catalyst deactivators (Hahladakis et al., 2018; Groh et al., 2019). 2naphtylamine (a potent carcinogen to humans) (Bie et al., 2017), and aminocaproic acid (a hydrolytic enzyme inhibitor which can inhibit the phase I biotransformation in biota (Purwin et al., 2017)) were also found in the F1 fraction (Fig. 3).

The F1 and F2 fractions had the Top 1 and Top 2 chemical entity numbers among the ten fractions, with 808 and 635 entities, respectively, which seems to be responsible for their high acute toxicity in bioassays. However, the toxicity for different fractions was not completely dependent on the overall number of chemicals. For example, the SF2.1 subfraction had 808 entities, but it exerted much lower lethality ($10 \pm 10 \%$) and did not alter heart rate ($60 \pm 6 \text{ times/min}$) nor hatching rates ($31 \pm 18 \%$) (Fig. S3). Similarly, SF2.2 had the second most entities among subfractions with 635 entities but did not cause lethality or sub-acute toxicity. This may be because that most of the entities found in the fractions are ethylene (C_2H_4) derived polymers that make up the plastic (Fig. S4), and the toxic effects shall be mainly determined by the properties of the pollutants.

3.3. Environmental significance

In this study, we find that the toxicity of plastics may not only be solely due to its physical impairment. Multiple estrogenic active substances exist within plastics and may cause estrogenic effects in some leaching scenarios. Of additional concern was the huge number of largely uncharacterized chemicals in plastics, with more than 4,700



Fig. 3. The identified chemical entity compositions based on intensities in four fractions. F1: fraction 1; F2: fraction 2; F6: Fraction 6; F9: fraction 9. Every circle in the figure characterizes 1% intensity of the total identified chemical intensities in each fraction (each identified chemical has more than 5-fold higher intensity than that in the procedural control). The total chemical entity intensity constitutes 18.1‰, 24.6‰, 10.6‰, and 16.9‰ of the total fraction intensities, respectively. The identified chemical entity compositions based on entity numbers can be found in Figure S5.

entities found on this single-use plastic item. Even though many of the chemicals were chains having the repeat unit $[CH_2]$, we still identified a variety of catalysts, dyes, antioxidants, intermediates, and antibacterial agents in different fractions. Besides, plasticizers, bisphenols, and other estrogenic chemicals were identified in fractions with higher logKow values suggesting absorption from the gastrointestinal tracts of fish may be rapid. The more polar substances (especially existing in the first two fractions) also migrated into the surrounding environment following simulated digestion easily. Absorption and resulting toxicity of most of these materials in biota are generally unknown, and given the detection of these substances in the digest, additional studies are warranted. As this study only targeted estrogenic and developmental responses in fish, additional biological targets may also need to be examined to better characterize the potential risks of plastics to biota.

CRediT authorship contribution statement

Qiqing Chen: Methodology, Writing - original draft, Formal analysis, Investigation, Writing - review & editing. Mauricius Marques dos Santos: Methodology, Writing - original draft, Formal analysis, Writing - review & editing. Philip Tanabe: Methodology, Resources, Writing - review & editing. Gary T. Harraka: Investigation, Writing review & editing. Jason T. Magnuson: Investigation, Writing - review & editing. Victoria McGruer: Methodology, Writing - review & editing. Wenhui Qiu: Methodology, Writing - review & editing. Huahong Shi: Writing - review & editing. Shane A. Snyder: Supervision, Writing review & editing. Daniel Schlenk: Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jhazmat.2020.123421.

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