Green Chemistry

CRITICAL REVIEW

View Article Online
View Journal | View Issue



Cite this: *Green Chem.*, 2017, **19**, 4234



# A multidisciplinary investigation of the technical and environmental performances of TAML/peroxide elimination of Bisphenol A compounds from water†‡

Yusuf Onundi,[a] Bethany A. Drake,[b] Ryan T. Malecky,[b] Matthew A. DeNardo, *[b] Matthew R. Mills, [b] Soumen Kundu,[b] Alexander D. Ryabov,*[b] Evan S. Beach, [b] Colin P. Horwitz,[b] Michael T. Simonich,[c] Lisa Truong, [c] Robert L. Tanguay, *[c] L. James Wright,*[d] Naresh Singhal *[a] and Terrence J. Collins *[b]

Designing technologies that mitigate the low-dose adverse effects of exposures to large-volume, every-day-everywhere chemicals such as bisphenol A (BPA, **1a**) requires an understanding of the scope of the exposures and the nature of the adverse effects. Therefore, we review the literature of, (i) the occurrences of **1a** in humans, waters and products and the effectiveness of widely deployed mitigation methods in **1a** stewardship and, (ii) the adverse effects of **1a** exposures on human cells and fish. Within this broad context, we present and evaluate experimental results on TAML/$H_2O_2$ purification of **1a** contaminated waters. TAML/$H_2O_2$ catalysis readily oxidizes BPA (**1a**) and the ring-tetramethyl (**1b**), tetrachloro (**1c**), and tetrabromo (**1d**)-substituted derivatives. At pH 8.5, TAML/$H_2O_2$ induces controllable, oxidative oligomerisation of **1a** (2-, 3-, 4-, and 5-unit species were identified) with precipitation, establishing a green synthetic pathway to these substances for biological safety characterisation and an easy method for near quantitative removal of **1a** from water. TAML/$H_2O_2$ (24 nM/4 mM) treatment of **1a** (10 000 μg $L^{-1}$) in pH 8.5 (0.01 M, carbonate) lab water effects a >99% reduction (to <100 μg $L^{-1}$ **1a**) within 30 min. Yeast oestrogen screens (YES) of the pH 8.5, TAML/$H_2O_2$ treated, catalase quenched, and filtered oxidation solutions show elimination of **1a** oestrogenicity. Zebrafish developmental assays of TAML/$H_2O_2$ treated, unfiltered, agitated pH 7, **1a** solutions showed no significant incidences of abnormality among any of 22 endpoints—treated samples showed an insignificant increase in mortality. At pH 11, the TAML/$H_2O_2$ oxidations of **1a–d** are fast with second order rate constants for the substrate oxidation process ($k_{II}$ values) of (0.57–8) × $10^4$ $M^{-1}$ $s^{-1}$. The **1a** oxidation gives CO and $CO_2$ (~78%), acetone (~25%) and formate (~1%). In striking contrast with pH 8.5 treatment, no oligomers were detected. TAML/$H_2O_2$ (150 nM/7.5 mM) treatment of **1a** (34 244 μg $L^{-1}$) in pH 11 (0.01 M, phosphate) lab water effected a >99.9% reduction (to <23 μg $L^{-1}$ **1a**) within 15 min. The pH dependent behaviour of **1a** was examined as a possible origin of the differing outcomes. The 1st and 2nd p$K_a$ values of **1a** were estimated by fitting the pH dependence of the UV-vis spectra (p$K_{a1}$ = 9.4 ± 0.3; p$K_{a2}$ = 10.37 ± 0.07). At pH 8.5, coupling of the radical produced on initial oxidation evidently outcompetes further oxidation. A linear free energy relationship between the logarithm of the pH 11, $k_{II}$ values and the redox potentials of **1a–d** as determined by differential pulse voltammetry in $CH_3CN$ is consistent with rate-limiting, electron transfer from the dianionic

Received 12th May 2017,
Accepted 19th July 2017

DOI: 10.1039/c7gc01415e

rsc.li/greenchem

[a]*Department of Civil & Environmental Engineering, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand*
[b]*Institute for Green Science, Department of Chemistry, Carnegie Mellon University, 4400 Fifth Avenue, Pittsburgh, Pennsylvania 15213, USA*
[c]*Department of Environmental and Molecular Toxicology, Sinnhuber Aquatic Research Laboratory, Environmental Health Sciences Center, Oregon State University, 28645 East HWY 34, Corvallis, OR 97333, USA*
[d]*Centre for Green Chemical Science, School of Chemical Sciences, University of Auckland, Private Bag 92019, Auckland 1142, New Zealand.*
*E-mail: lj.wright@auckland.ac.nz; Tel: +64 9923 8257*

†We dedicate this publication, which has occupied us for 15 years, to the memory of our great friend and extraordinary visionary into endocrine disruption, Dr Theodora Emily Decker Colborn (b.1928–d.2014), to our brilliant colleague who coined the term 'Endocrine Disruption', Dr Pete Myers, and to the great father of BPA low dose toxicity research, Prof. Frederick S. vom Saal—their work (and that of other ED researchers) can arm all chemists with a better understanding of the relationships between everyday-everywhere chemicals and the future good to inspire proactive advances in sustainable chemistry.

‡Electronic supplementary information (ESI) available. See DOI: 10.1039/c7gc01415e

form of **1a** at pH 11, followed by a multistep, deep degradation without observation of 4-(prop-1-en-2-yl) phenol **12**, a common **1a** oxidation product—an improved synthesis of **12** is described. Microtox® analyses of pH 12, TAML/$H_2O_2$ treated **1a** solutions showed significantly reduced toxicity. The facility and high efficiency by which TAML/$H_2O_2$ catalysis eliminates **1a** from water, by either mechanism, suggests a new and simple procedure for **1a** stewardship.



## Introduction

Green Chemistry has much to offer at every stage of the lifecycle of chemical products and processes. Both during and at the end of commercial utility, many chemical products become water contaminants.[1,2] These may or may not be persistent. Those that negatively impact flora or fauna at low concentrations (ng $L^{-1}$–μg $L^{-1}$) are called "micropollutants" (MPs). Some MPs are endocrine disruptors (EDs). An endocrine disruptor is, "an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action".[3] Minimizing exposures to EDs is a significant sustainability challenge. High volume EDs that sufficiently elude water treatment processes to threaten the environment and human health are among the most difficult MPs to manage.[4,5] For example, phenolic compounds are not completely removed by the combined physical, biological and chemical processes in water treatment plants resulting in contamination of released effluent streams.[6,7]

Bisphenol A (2,2-bis(4-hydroxyphenyl)propane, BPA, **1a**, Fig. 1) is one such continually emitted, anthropogenic, xeno-oestrogenic, high volume, commodity, phenolic ED found in multiple products.[8–11] Although **1a** is often regarded as weakly oestrogenic, its capacity to impact biological processes is modulated by several factors including interactions with plasma oestrogen-binding proteins,[12,13] varying potential for metabolism,[13–19] and the types and quantity of oestrogen receptors (ERs) present, including those bound to membranes.[20,21] In some cases, **1a** has been shown to have the same effect as and be as potent as the endogenous, primary, female sex hormone oestradiol (E2, Fig. 1),[3,13,20,22,23] which can alter the functioning of cellular proteins at sub-picomolar to nanomolar concentrations.[13,24] Oestrogens regulate development[25–27] and actions in bone, brain, cardiovascular, liver, and reproductive tissues.[28] ERs are targeted by some endogenous hormones and pharmaceuticals. Such drugs include oestrogens, anti-oestrogens and selective oestrogen receptor modulators like **1a**,[13] which lack the steroid ring structure of oestrogens (see E2, Fig. 1), but retain structural elements necessary to bind to ERs.[28,30] Drugs that target ERs include fertility enhancers and contraceptives, as well as menopausal hormone,[31] breast[32] and prostate cancer[33,34] therapeutics. In addition to acting as an oestrogen, **1a** can act as a thyroid hormone[35,36] and androgen.[37] Inappropriate adjustment of oestrogen, thyroid hormone and androgen regulated processes, such that which can result from exposure to xeno-oestrogens like **1a**, can have negative effects.[20,25–27,31,38–44] Consequently, in 2016 the European union voted to recognize **1a** as a presumed human reproductive toxicant.[45] In 2017, it voted to also add **1a** to the list of substances of very high concern for adverse effects on human mammary gland development, cognitive functions and metabolism, identifying it as a general disruptor of the human endocrine system.[46]

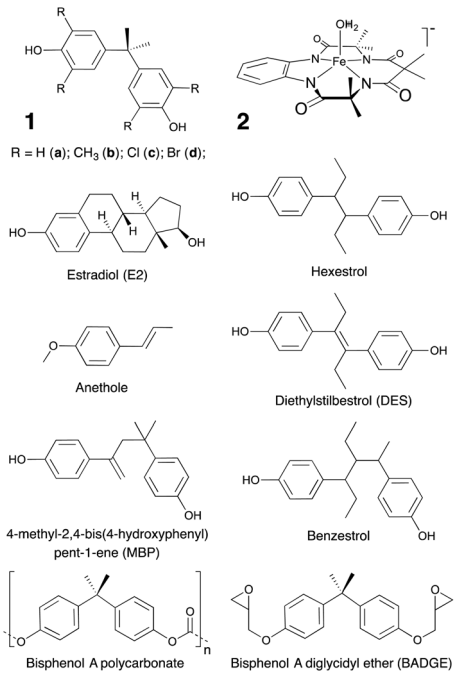



**Fig. 1** Bisphenol A (BPA, **1a**), its derivatives (**1b–d**) and the TAML activator (**2**) used in this work, as well as compounds referred to in this work. TAML is a registered trademark of Carnegie Mellon University covering tetra-organic-amido-*N* macrocyclic ligand complexes.[29]

Approximately 15 billion pounds of **1a** are produced annually.[1] This figure is expected to increase with a compound annual growth rate (CAGR) of almost 6% by 2020.[47] About 95% of the **1a** produced is incorporated into BPA polycarbonate plastic and bisphenol A diglycidyl ether (BADGE) epoxy resins[48] (Fig. 1), including those used to line food and water containers such as metal cans,[49,50] metal and concrete drinking water pipes[51,52] and residential water storage tanks.[52,53] BPA is also added to phenoxy,[54] polyacrylate,[55,56] polyarylate,[57,58] polyetherimide,[58] polyester,[55,56,58,59] polyester–styrene,[55] and polysulfone[54,56,58,59] plastic and resins,[54] and rubber, polyethylene tetraphthalate,[13,54,55,59] and polyvinyl chloride (PVC) products where it can function as a stabilizer,[54,60,61] antioxidant[62,63] or inhibitor of end polymerization.[64]

Many of these products leach **1a** to contribute to ubiquitous environmental contamination.[50,53,65] For example, 7.8 μg $L^{-1}$

of **1a** was detected in the water of an epoxy resin lined drinking water tank,[66,67] the contents of canned goods have been estimated to contain 4–23 μg of **1a** as a result of leaching from the epoxy resin can linings,[50,68] and, at room temperature, polycarbonate food containers have been estimated to be capable of leaching *ca.* 6.5 μg of **1a** into each gram of food stored inside.[68,69] Aqueous **1a** concentrations of 1.98–139 μg $L^{-1}$ have been found to result from the room temperature soaking of each of one gram of PVC products and synthetic leather for two weeks in the dark.[60,67] Room temperature, 24-hour exposure of pure water to PVC hoses resulted in leaching of 4–1730 μg $L^{-1}$ of **1a**.[67,70] Contamination also occurred upon passage through the tube and increased from 8.7–558 μg $L^{-1}$ as the water residence time increased from 0–24 hours.[70] At 20 °C, polycarbonate tubes leach **1a** into lab, river, and sea waters at rates of 0.15, 0.2, and 1.6 μg $L^{-1}$ $day^{-1}$, respectively—the amount of **1a** leached is less than that from PVC hoses.[67,70,71]

Herein we examine the consequences of widespread BPA use and present an enticing laboratory study of a potential method for BPA stewardship. The impacts of BPA use are presented in two parts, a 'Mini-Review of the occurrence of BPA' and a 'Mini-Review of BPA toxicity'. These draw extensively upon reviews both from within and outside of traditional chemistry.[1,10,11,13,25,28,48,49,68,72–109] The BPA occurrence mini-review encompasses the industrial synthesis and associated releases, the diverse product space, the associated contamination of air, water, soils, food crops, and recycled products, and measured human body burdens. The immense scope of BPA use and contamination is detailed to highlight the complexity of the stewardship challenge. Thus, the design and implementation of sustainable, chemical processes for removing BPA from waters is an important goal for green chemists. Therefore, the technical performances of currently deployed BPA water treatment technologies are surveyed. The BPA toxicity mini-review outlines the health and ecological implications of exposures to BPA at the concentrations currently observed in humans and environmental waters. With this understanding, we evaluate the technical and environmental performances of TAML/peroxide (**2**/$H_2O_2$, Fig. 1) oxidation of heavily BPA-contaminated lab water at pHs 8.5 and >11 at similar concentrations to certain processing streams and landfill runoff. The TAML/peroxide processes are found to be remarkably simple and effective warranting further studies in a variety of real-world scenarios.

## Mini-review of BPA occurrences

This mini-review demonstrates the panoptic contamination of the ecosphere by BPA (**1a**) and **1a** removal by the water treatment strategies currently deployed. We have largely focused on the sources and surface water occurrences of **1a**. However, it is also important to recognize the significance of the reported contamination of oceans[110–112] and sediments.[11,67,113] The presence of polycarbonate in oceans is of special concern because leaching of **1a** from polycarbonate occurs more rapidly in sea than in fresh waters,[74,114] **1a** oxidation by radical oxygen species is slower in seawater than in control water,[71] and marine bacteria strains have been found to degrade **1a** much more slowly than freshwater strains.[107,115] Furthermore, **1a** has been detected in marine organisms including phytoplankton, zooplankton, mussels, herring, flounder, and cod, and bioamplification between phytoplankton and zooplankton has been documented.[110,111,116]

The reported sediment contamination levels exceed those of both sea and fresh water.[67] This assessment is consistent with the observation of higher concentrations of **1a** in the lower layer of water columns than in the upper layers and a positive correlation between the low layer and sediment concentrations.[117] Since **1a** degradation is slower under anaerobic than aerobic conditions,[67,109,117,118] and agents in the environment accumulate in the accessible reservoir in which they have the longest half-life and that reservoir then becomes a secondary source of emissions,[119] the potential for rerelease of sediment-bound **1a** is concerning. A report on the fates of plastics and the need for reforms has recently been released.[113]

Biomonitoring studies have revealed that **1a** is also a pervasive human contaminant—unconjugated **1a** has been detected in foetal, child and adult fluids and tissues (central tendency: 0.3–4.4 μg $L^{-1}$ or 1.3–19 nM).[120] Total (unconjugated + bioconjugated) **1a** urinary concentrations have been detected in 92.6% of 2517 Americans older than 6 years (mean: 5.2 μg $L^{-1}$ or 23 nM, range: 0.3–149 μg $L^{-1}$ or 1.3–653 nM).[121] Concentrations have been found in human colostrum (total **1a**, all samples, 1–7 μg $L^{-1}$, mean of 3.41 μg $L^{-1}$)[122] and breast milk (total **1a**, 90% of samples, <0.3–6.3 μg $L^{-1}$, mean of 1.3 μg $L^{-1}$).[123] Breast milk concentrations were found to rise from 6.2 μg $L^{-1}$ to *ca.* 30 μg $L^{-1}$ one hour after consumption of a canned coffee drink containing 37.4 μg,[124] indicating that exposure of mothers correlates with that of nursing children. An overview of the available science on the impacts of human exposures to these concentrations is presented later in the 'Mini-Review of BPA toxicity'.

The concentrations found in humans, colostrum, and breastmilk are comparable to some of the higher surface water concentrations of **1a** that have been reported throughout the globe (US: median of 0.14 and maximum of 12 μg $L^{-1}$;[125] Atibaia River watershed of São Paulo, Brazil: weighted average of 4.6 and maximum of 13 μg $L^{-1}$;[126] Dongguan watershed of China: average of 6.5 and maximum of 56 μg $L^{-1}$;[127] Nagara River of Japan: average of 4.8 and maximum of 22.2 μg $L^{-1}$;[117] and Portugal: 0.07–4 μg $L^{-1}$).[128] An overview of the available science on the impacts of fish exposures to these concentrations is also presented in the 'Mini-Review of BPA Toxicity'.

Human exposure to **1a** is continuous and occurs through numerous known and unknown routes.[78,79] While municipal drinking water itself is not typically considered a major source of **1a** (France 2011: <9–50 ng $L^{-1}$;[129] Germany 2000: 0.003–2 ng $L^{-1}$;[130] Malaysia 2009: 3.5–59.8 ng $L^{-1}$;[131] Spain 2003: <5–25 ng $L^{-1}$),[132] significantly higher drinking water concentrations have been reported (Nigeria 2015: 109.00–882.50 μg $L^{-1}$).[133] Removal of **1a** by conversion to transformation pro-

ducts,[129] including **1c** (Fig. 1),[134,135] during disinfection by chlorination prior to release may contribute to the reported, low drinking water **1a** concentrations. The potential human health and environmental impacts of exposure to **1a** chlorination products are briefly discussed later in this work. The higher reported **1a** drinking water concentrations derive from both a higher initial **1a** concentration and contributions from plastic storage container leachate.[133] Passage through tap mounted filter devices,[131] pipes lined with epoxy resin, or polycarbonate or PVC tubing can also raise **1a** concentrations.[129] Ingestion of leachate[50,136] from polycarbonate,[137,138] epoxy[53,62,136] and organosol[62,139] resins such as those made from bisphenol A diglycidyl ether (BADGE, Fig. 1), and **1a** stabilizers and antioxidants[62,63] in, for example, food contact papers,[140] PVC stretch films,[141] dental sealants,[80,101,142–151] and food and drink containers[49,50,52,63,139,152–156] including commercial polycarbonate containers used for microwave ovens,[69] adult[131,152] and baby[52,133,157–162] water bottles and cans[50,52,163] is the most authoritatively documented route of human **1a** exposure.

Canned goods are perhaps the most well-studied source of dietary **1a**. Globally, contamination with **1a** has been detected in canned beers,[154] decaffeinated and non-decaffeinated coffees,[162,164] soft drinks[165,166] including diet and regular ginger ales, diet and regular root beers,[165] diet and regular colas,[154,165] energy drinks,[154,165] orange and lemon soft drinks,[154] flavoured and unflavoured soda waters,[165] teas[162,165] and tonic waters,[165] infant[167–169] and follow up formulas,[170] the liquid phases of canned artichokes, green beans, corn, mushrooms, peas, and mixed vegetables,[50] the homogenized liquid and solid contents of canned fruit products including coconut cream,[154,171] coconut milk,[156] lychees, mangoes,[154] olives,[171] peaches, light pineapples,[154] tomatoes,[63,155,156,171] tomato juice[156] and tomato paste,[172] and fruit pieces and cocktails,[63] the homogenized liquid and solid contents of canned vegetable products including asparagus,[156] baked beans in tomato sauce, green beans,[63] beetroot,[171] carrots,[63] corn,[63,171,172] mount elephants, mushrooms,[156] peas,[63,171] jalapeño peppers,[153] potatoes,[63] and goulash,[154] the homogenized liquid and solid contents of canned soups[171,172] including cream of chicken, chicken and white wine,[63] potato,[154] tomato,[63] and Tom Kha,[154] the homogenized liquid and solid contents of canned sauces[171] of many varieties including demi-glace, fond de volaille, gratin, meat, tomato, and white,[156] the homogenized liquid and solid contents of canned pastas in tomato sauce,[63] the homogenized liquid and solid contents of canned seafood including Japanese sand lance, mackerel,[156] pilchards in tomato sauce,[63] salmon,[63,156,171] sardine,[156] sardine in tomato sauce[63] shrimp, squid,[156] tuna,[156,171,172] and fish and vegetable mixtures,[156] the homogenized liquid and solid contents of canned meats[171] including chicken, corned beef, fish balls, ham, hot dogs, and pork,[63] the homogenized liquid and solid contents of canned quail eggs,[156] the homogenized liquid and solid contents of desserts including evaporated milk[63,173] and creamed rice,[63] the solids of canned crushed tomatoes, young peas,[154] corn,[154,174] haricot beans, red kidney beans, lentils,[154] mushrooms,[174] tuna in oil, and sardines in oil,[154] mackerel filet in tomato sauce, and canned dinners.[166] Contamination of vegetable solids has been found to be greater than that of the liquids.[174]

Alone, the estimated child and adult dietary intakes (0.008–14.7 μg $kg^{-1}$ $day^{-1}$)[82] are unlikely to account for the concentrations observed in human bloodstreams.[79] The human oral dosage necessary to maintain the average unconjugated **1a** blood concentrations observed in healthy adults, adults having diseases, pregnant women, and foetuses (0.5–10 μg $L^{-1}$, average *ca.* 1–3 μg $L^{-1}$, greater than that found in most surface waters) has been estimated at >500 μg $kg^{-1}$ $day^{-1}$.[81] This estimate agrees with a prediction of an oral dose of 1.43 mg $kg^{-1}$ $day^{-1}$ for 10 days as necessary to effect human steady state blood levels of 0.9–1.6 μg $L^{-1}$.[175] Therefore, alternate routes of exposure which obviate the first pass metabolism of the liver that greatly reduces blood concentrations of unconjugated **1a**,[79] including dermal uptake, which increases when skin is wet and/or greasy,[176,177] and sublingual absorption[78,79] are thought to contribute to human blood concentrations of **1a**. For example, the handling of thermal receipt papers, which are coated in amounts of unbound **1a** that have been found to be at least one thousand times greater than that of food can epoxy linings,[178] is the most well-known route of dermal exposure.[140,177,179–182]

Given the myriad of products into which **1a** is incorporated or contaminates, and the known sublingual, oral and dermal routes of exposure, other less-discussed sources likely also contribute to human blood concentrations of **1a**. While not directly proven to raise blood concentrations of **1a**, it is reasonable to expect additional exposures from, *inter alia*, indoor and outdoor air,[183–186] indoor dust,[183–185,187–189] 5 gallon water carboys,[157] polyethylene tetraphthalate[13,132,190] and polycarbonate water bottles,[129] drinking water generators[52] and pipes,[51] water main[55] and tap[131] filters, fungicides,[54,55,59] randomly selected fresh foods including fresh cherries, courgettes, eggplants, medlars, oranges, peaches, peppers, and tomatoes,[191] white clams, crabs, blood cockles, fish, prawn, and squid,[111] buns, flour, hard cheese, minced meat, sausages, hamburgers, sliced salami and turkey, and frozen pizza in plastic packaging, bread in plastic or paper packaging, liver paté in plastic packaging with metal foil, fish pudding in plastic or paper packaging, caviar spread in a metal tube, jam in glass jars with metal or plastic screw caps, whole eggs packaged in cardboard,[166] honey packaged in glass or plastic that was imported in epoxy-lined metal drums,[192] baby food products in glass[193] and high-density polyethylene plastic[168] jars[52] with metal lids, solid[185] and liquid foods served at day care centers,[183,184] baby teethers,[194] breastpumps,[52] children's books and toys,[52,195,196] cosmetics,[197] training cups,[157] dishwasher and laundry detergents,[198] protective and general sporting equipment,[52,79] inhaler housings, musical instrument mouthpieces,[52] plastic plates and utensils[52,79,133] including those used at elementary schools,[162] nail polish,[55,198] pillow protectors,[198] outdoor play area soil,[183] artificial teeth,[55] hand, hard floor surface and food preparation surface wipes,[184] personal care-hygiene pro-

ducts[198,199] including cleansers, conditioner, shaving cream, lotions, shampoo, bar soap, sunscreen,[198] toothbrushes,[133,198] toothpaste,[133] and face and body washes,[198] automotive interiors and exteriors including bumpers, interior light covers, dashboards, radiator grills, fog lamps, headlight lenses, head, brake and tail lights, indicator reflectors, roofs, windows, covers, and coatings,[52] building materials[52,91] including structural adhesives and fillers, coatings, carport covers,[52] flooring,[52,55] architectural, conservatory, greenhouse, and bus stop shelter glazings, grouting, mortars, concrete reinforcement, sheets for roofing,[52] ceiling tiles,[133] and road and train track noise reduction walls, the casings of cameras, computers, copiers, monitors,[52] phones,[52,133] pens,[121] steamirons, suitcases, and TVs,[52] paper currencies,[200] CDs[52,55,60,79] and DVDs,[52,79] hair dryers,[52] cigarette filters,[201] contact lens holders,[52] eyeglass frames,[79] lenses[52,91,133] and nosepads,[79] razors,[52] cellulose products including chromo board,[202] business cards,[140] catalogues,[202] coatings, dye developers,[91] mailing envelopes,[140] magazines,[140,202] carbonless copy paper,[203] free advertising papers, and advertising supplements,[202] recycled cellulose fiber (RCF) products including newspapers,[140,202,204] napkins,[140] paper towels,[140,205] toilet tissue,[140,202] and paperboard[140,202] including the food contact surfaces of confectionary, fried chicken, fried potato,[204] pizza,[204,206] sandwich,[204] and general food storage boxes[202] as well as noodle cups,[204] virgin paper products including coffee filters, cooking papers, cups, dishes, napkins, tea bags, tissues, and fried chicken wrapping paper,[204] the epoxy paints,[52,207,208] coatings and composites of aircraft, car, boat,[52] and DIY repair adhesives[52,91] and fillers, household appliances including vacuum cleaners, dishwashers, dryers, fridges, freezers, and washing machines, windmill blades, engine blocks, concrete and steel bridges, gas bottles, aircraft, boats, buses, canoes, caravans, cars, helicopters, mobile homes, railcars, yachts, general cans including those containing oils and hairsprays, caps, closures and crown corks, general and sea containers, cookers, decking, drums, heat, ventilation and air conditioning equipment, steel frames, furniture and racks, office furnishings, underwater ship hulls, printing inks, cargo and storage tank linings, primed metals, electric motors, engines, machinery, and parts, pails, automotive body, construction cladding, metal roofing, ceiling, and garage door panels, automotive and electronic parts, pipes, valves and fittings, gas pipes, offshore drilling platforms, general plastics, radiators, concrete reinforcing rebars, traffic light reflectors, roadsigns, emissions scrubbers, supporting steel structures including bars, beams, gratings, rods, and shafts, metal and concrete storage tanks, menus, and food trays, gardening tools and equipment, collapsible tubes including those containing creams and toothpastes, paper and board varnish including food packaging, secondary containment walls, and wood, medical equipment including ampoules, i.v. connectors, dialysers, medical packaging film, blood oxygenators and sample reservoirs, cardiotomy reservoirs, respirators,[52] single use surgical tools,[52] and medical tubing,[13] the polycarbonate plastics, resin linings, and printed circuit boards of electronic products[52,60,209,210] and electronic waste,[60,91,209] distributor boxes, plug connectors, large advertising displays, fuses, lamp globes, inductors, lamp holders, lamps, electrical meters, switch modules, solar panels, sockets, streetlights, battery power stations, switches, transformers, kitchen tools and appliances including front panels for electric cookers,[52] refrigerator crisper drawers,[55] electrical kettles, coffee makers, microwaves, mixers,[52] and food processors,[55] and PVC products[48,60] including synthetic leather[211–213] in, for example, seating materials and clothing,[214] shower curtains,[198] and cord coverings.[60,211] It is important to note that the concentrations found can be high. For example, a Nigerian study recorded in the occurrences above reported **1a** contamination ranges in consumer products and food/drink samples of 915.00–1415.50 μg $L^{-1}$ and 163.00–2785.00 μg $L^{-1}$, respectively.[133]

When used, discarded or recycled, **1a**-containing goods and the contaminated solutions generated in the manufacture and processing of **1a** and **1a**-containing goods, become the largest sources of **1a** in the environment.[60,211,215,216] In 2008, the government of Canada concluded that "bisphenol A is entering or may be entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or constitute or may constitute a danger in Canada to human life or health".[217] Consequently, in 2009, it recommended **1a** releases be reduced to the lowest level technically and economically feasible and proposed an upper limit of 1.75 μg $L^{-1}$ in emissions.[218] This value was chosen because it is an order of magnitude greater than the 2009 partial no effect concentration (PNEC) of **1a**[218]—it has been argued that the PNEC for **1a** in surface waters should be lowered to 0.06 μg $L^{-1}$,[219] and a maximum concentration of 0.03 μg $L^{-1}$ has been proposed to safeguard 95% of exposed species from the chronic toxicity of **1a**.[74] Therefore, easy to implement, safe technologies like the potential process documented in this contribution are critical to achieving emissions standards that, like the proposed Canadian standard of 1.75 μg $L^{-1}$, safeguard human health and the environment.

In 2014, the 258 million tons (mt) of municipal solid waste generated in the US before recycling, composting or combustion was composed of 69 mt of paper and paperboard (28% of which was landfilled, 65% was recycled and 7% was combusted), 33 mt of plastics (76% landfilled, 10% recycled and 15% combusted), 16 mt of textiles (65% landfilled, 16% recycled and 19% combusted), and 8 mt of rubber and leather (51% landfilled, 18% recycled and 32% combusted).[220] Landfilled postconsumer goods release **1a**.[211] Consequently, water that has contacted waste, known as landfill leachate[221,222] (mostly pH 6.5–8.5),[61,89] has been reported to be a major source of **1a** in the environment[202,215] (Germany 2002: 4200–25 000 μg $L^{-1}$, average of 14 067 μg $L^{-1}$;[223] Germany 2003: *ca.* 500–5000 μg $L^{-1}$;[224] Japan 1999: *ca.* 500–7500 μg $L^{-1}$;[225] Japan 1996: <0.5–17 200 μg $L^{-1}$, median of 269 μg $L^{-1}$;[211] Norway 2015: 0.7–200 μg $L^{-1}$, average of 66.5 μg $L^{-1}$;[226] Philippines 2003: *ca.* 9000 μg $L^{-1}$;[54] and Sweden 2000: 4–136 μg $L^{-1}$).[227] These mixed pollutant streams containing **1a**

may or may not be treated based on local judgments of the need for such.[54] Treatments often include recycling through the landfill, on-site biological treatment,[90] coagulation, filtration, and/or activated carbon adsorption,[54,89] prior to discharge to surface waters or a municipal WWTP.

For surface water discharges, a higher treatment requirement often applies. One such treatment process entails pumping collected leachate containing *ca.* 100 μg $L^{-1}$ **1a** into an adjustment tank where it is combined with leachate of unreported **1a** concentration from four other landfill blocks and from neighbouring landfill sites and aerated. This reduced the concentration of **1a** to *ca.* 0.15 μg $L^{-1}$. This combined influent was further treated by phosphate addition and passage through three biological contactors, coagulation with $FeCl_3$ and NaOH, mixing, sedimentation, and sterilization prior to discharge into a river.[61] When operated at *ca.* 25 °C, the stages of the treatment process that followed combination with leachate of undisclosed composition and aeration removed *ca.* 80% of the influent *ca.* 0.15 μg $L^{-1}$ **1a** and produced effluents of *ca.* 0.03 μg $L^{-1}$. Biological treatment and coagulation followed by sedimentation each account for roughly half of the amount of **1a** removed. When the process was operated at *ca.* 20 °C, the effluents were found to contain higher concentrations of **1a** than the post-aeration influents. Both biological treatment and coagulation produce contaminated secondary wastes that must be landfilled, which risks rereleases of **1a**, or incinerated.

Another treatment entailed **1a** removal through the use of a membrane bioreactor (MBR) consisting of three activated sludge tanks. The first two tanks engaged nitrifying bacterial cultures ($NH_3 \rightarrow NO_3^-$). The third engaged a denitrifying culture ($NO_3^- \rightarrow N_2$). This was followed by ultrafiltration (UF).[224] The influent *ca.* 500 μg $L^{-1}$ **1a** was reduced to *ca.* 300 μg $L^{-1}$ by the biological treatment of the MBR and the subsequent UF of the MBR effluent reduced this to *ca.* 2 μg $L^{-1}$. Biological treatment and UF produce secondary wastes in the forms of contaminated sludge and retentate, respectively, that must be landfilled, which risks rerelease of **1a**, or dried and incinerated. Further treatment by nanofiltration (NF) increased the MBR effluent concentration of **1a** to *ca.* 3 μg $L^{-1}$. Ozonation (0.2–0.5 kg $O_3$ per kg COD) of the NF retentate, which contained *ca.* 4 μg $L^{-1}$ **1a**, removed *ca.* 83% to give effluent containing *ca.* 0.7 μg $L^{-1}$.

For discharge to municipal WWTPs, a lower treatment requirement often applies. One such treatment entailed collection of the raw leachate in a regulating reservoir for pumping through a sequence of adjustment and aeration, mixing and sedimentation tanks before discharge into a sewer.[61] About 30% of the influent *ca.* 90 μg $L^{-1}$ **1a** was removed giving effluents of *ca.* 65 μg $L^{-1}$. Another treatment entailed passage through a MBR which is similar to that discussed previously.[224] The biological treatment of the MBR reduced the highly contaminated, *ca.* 5000 μg $L^{-1}$ **1a**-containing leachate to *ca.* 1300 μg $L^{-1}$. This was further reduced to *ca.* 70 μg $L^{-1}$ by UF. Further treatment by passage through a granular activated charcoal (GAC) column removed *ca.* 50% of the remaining **1a**, resulting in final discharges of *ca.* 35 μg $L^{-1}$. GAC treatment produces contaminated GAC which, when removal performance diminishes due to saturation, must be landfilled with risk of **1a** rerelease and replaced at cost, or thermally regenerated.

In addition to landfill leachate, other process and waste streams containing **1a** in excess of 1.75 μg $L^{-1}$ have been reported worldwide. Some are treated before release and some are not. For example, **1a** has been detected in untreated paper production and recycling solutions (Spain 2004: 3.0–142 μg $L^{-1}$, mean of 53.6 μg $L^{-1}$).[228] Primary and secondary treatment at the plant reduced these **1a** concentrations to 1.6–27 μg $L^{-1}$ (mean of 13.8 μg $L^{-1}$).[228] At various times, **1a** concentrations have been reported to be high in final effluents of the chemical (Austria 2000: 2.5–50 μg $L^{-1}$, mean of 18 μg $L^{-1}$),[229] paper production and recycling (Austria 2000: 28–72 μg $L^{-1}$, mean of 41 μg $L^{-1}$;[229] Japan 2002: 0.2–370 μg $L^{-1}$, mean of 59 μg $L^{-1}$),[230] plastics manufacturing and recycling (Nigeria 2015: 108–163 μg $L^{-1}$, mean of 130 μg $L^{-1}$),[133] and industrial laundry (US 2008: 21.5 μg $L^{-1}$)[231] industries. Unfortunately, we were unable to locate data on the concentrations of **1a** in various other industrial solutions and effluents including washing residue and wastewater generated in the production of **1a** itself[91] and the sink-float/heavy media separation slurries, chemical etchants, detinning, and chemical delacquering solutions employed in the recycling of, for example, cans and bulk metals.[102] As with landfill leachate treatment plant effluent, industrial effluents may or may not be treated before release to the environment or wastewater treatment plants (WWTPs).[216]

When directed to WWTPs, treated or untreated landfill leachate and industrial effluents may join with domestic wastewater which often also contains **1a**. For example, the use of toilet tissue made from recycled paper has been estimated to contribute *ca.* 36 000 pounds of **1a** to wastewater per year.[202,232] Consequently, at various times, **1a** concentrations in WWTP influent have been reported to be high (Austria 2000: 10–37 μg $L^{-1}$, mean of 21 μg $L^{-1}$;[229] Canada 2004: 0.16–28.1 μg $L^{-1}$;[233] Germany 2008: <0.02–12.2 μg $L^{-1}$, weighted average of 3.67 μg $L^{-1}$).[234] Though the removals of EDs including **1a** have been observed to vary with the operating conditions,[216,235–237] conventional wastewater (pH 7–8) treatment processes have been reported to remove 82 ± 12% of influent **1a**.[87,233] Primarily, this removal occurs through sorption to primary sludge and sorption to activated sludge which may or may not be followed by biological degradation.[87,237,238] The final effluents are often discharged to surface waters.[233] Reports indicate that *ca.* 2% of the influent **1a** is not degraded by and, as a result, remains in the activated sludge, along with a mixture of other EDs, the mass-normalized concentrations of which are significantly greater than those typically found in effluents and surface waters.[5,95,98,216,239–243] As a consequence of lesser degradation in anaerobic than aerobic biological treatment, adsorption of several EDs, including **1a**, to sludge occurs to a greater extent in anaerobic treatment.[239] Therefore while the use of nitrifying cultures can provide cleaner

effluents,[244] these can come at the expense of increased sludge contamination.[202]

The contaminated sludge generated in biological treatment can also become a source of **1a**. Sludge concentrations of 0.10–3.2 × $10^7$ μg $kg^{-1}$ of dry weight have been reported.[11,245–248] While incineration is practicable, the high costs, technological demands, low to no energetic gain, concentration of hazardous metal content in the ash produced which is usually landfilled, air emissions, and negative public perception can hinder its deployment.[249] Consequently, the contaminated sludge is often disposed of by landfilling or application to agricultural lands and composting.[99] For example, in 2004 the US produced 7.18 × $10^6$ dry US tons of sewage sludge solids, 55% (3.95 × $10^6$ tons) of which was land applied,[250] and in 2005, the EU-27 countries produced *ca.* 10.96 × $10^6$ dry tons of sewage sludge solids, 41% (4.49 tons) of which was directed towards agricultural use.[99] These percentages are consistent with the 50% land application and 50% incineration reported in 2004 for the Canadian Ashbridges Bay, Humber and North Toronto WWTPs.[233] While the practice recycles nutrients and, thus, can enhance the sustainability of societies, land application of sewage sludge can increase the risk of ED rerelease to the environment[233] and contributes to ED contamination of soils.[5,238,251–256] This has led to a considerable literature of the effects on animals and their offspring that graze on pastureland amended with sludge containing multiple EDs.[95,257–267] Since these studies mostly concern multi-ED exposures, we consider this area outside the scope of the current mini-reviews. Sludge is the primary source of **1a** soil contamination.[238] If practiced for an extended period of time,[239,255,256] land application to agricultural soils may contribute to the aforementioned levels of **1a** detected in fresh produce.[191] Soil **1a** can partition into soil water[83] which, in turn, can result in contamination of leafy vegetables,[238,268] root crops[238] and cereal grains.[238] Unfortunately, while never applying sewage sludge or only applying decontaminated sewage sludge would limit soil concentrations of **1a**, this alone cannot ensure **1a**-free soil.

Ongoing global deposition from ubiquitous contamination[186] of the atmosphere[238] and irrigation with treated and untreated contaminated water also contribute to soil concentrations of **1a**.[70,268] Sources of atmospheric aerosol concentrations of **1a** include volatilisation during processing, handling and transportation of **1a** (at least 109 metric tons per year)[91] the open burning of municipal wastes (US: estimated to be >75 000 kg per year)[269] and plastics,[186] the thermal degradation of polycarbonate,[270–272] waste electrical and electronic equipment recycling, disposal and burning,[186,210] waste sorting facilities including metal shredders,[226] and landfills.[226] For example, **1a** is a major product of the depolymerisation of polycarbonate observed on heating to 475 °C in air,[272] and flash pyrolysis gas chromatography of polycarbonate at 500–850 °C shows the release of $H_2O$, $CO_2$, **1a**, phenol, isopropenyl phenol, and diphenyl carbonate in addition to higher molar mass compounds.[273–275] Resuspension of contaminated soil also contributes to atmospheric concentrations.[186]

In addition to contributing to dietary exposures, cured, epoxy resins made from the **1a**-containing prepolymer Bisphenol A diglycidyl ether (BADGE, Fig. 1), such as those used in the metal coatings of canned goods, may contribute to atmospheric concentrations of **1a** when thermally degraded. In studies of heating the purified, cured resins made from BADGE prepolymers, stepwise alterations occur as the temperature increases. From *ca.* 250–350 °C, evaporation occurs of the compounds encaged in the cured polymer, including unreacted modifiers such as diols, and residual prepolymer mono- and bis(hydroxyether)s of **1a**.[276,277] From 300–340 °C, thermal degradation begins and **1a** is a major product released along with smaller amounts of isopropenylphenol, isopropylphenol and phenol.[278] Up to 500 °C, there is very little decomposition of the **1a** moiety.[278] From 500–600 °C, aryl–alkyl ether bonds are further cleaved and **1a** remains a major product released.[276–279] At >600 °C, the release of high boiling pyrolyzates with epoxide end groups decreases markedly,[279] presumably giving a more **1a**-rich product mixture.

The heating of cured resins made from BADGE prepolymers occurs in the recycling of metals. In, for example, aluminium recycling, thermal decoating or delacquering of the shredded metal is commonly performed prior to melting.[102,103] Approximately 18 metric tons of scrap pass through each delacquering machine per hour.[103] There are two major thermal delacquering approaches for Used Beverage Cans (UBCs).[103] The first is based on conveying crushed and shredded UBCs through zones of increasing temperature, which may be fixed at 520 °C [103] or may progressively rise to *ca.* 540 °C.[280] The furnace temperatures must be maintained below *ca.* 566 °C to prevent ignition of the surface contaminants.[280] The second approach relies upon roasting the scrap in a rotary kiln through various temperature stages, the last of which occurs at near 615 °C, with recirculation of the produced combustion gases.[103] Consequently, the gases produced in the delacquering process can be rich in **1a**. These then may or may not be treated with activated charcoal[281] and/or lime or calcium carbonate[282] before or after passage through a baghouse filter followed by release *via* a high stack.[283] These purifications create contaminated materials which must be disposed of by, for example, landfilling or incineration.[282] Alternatively, the delacquering gases may be combusted.[282] Activated charcoal may, or may not, be added to the resulting flue gases[281] which are then purified by passage through a baghouse filter.[283] This creates contaminated activated charcoal. In either case, any compounds not sequestered or destroyed are released.

Despite the activated sludge removals, WWTP effluent concentrations of **1a** in excess of 1.75 μg $L^{-1}$, which are often discharged to surface waters, have been reported (Austria 2000: <0.5–2.5 μg $L^{-1}$, mean of 1.5 μg $L^{-1}$;[229] Canada 2004: 0.01–17.3 μg $L^{-1}$;[233] EU 2008: 3.13–45 μg $L^{-1}$;[284] 2008: <0.02–7.6 μg $L^{-1}$, weighted average of 0.52 μg $L^{-1}$;[234] US 1999: <0.01–2.7 μg $L^{-1}$).[285] While these alone are cause for concern, of perhaps greater concern are the by-products that can be formed at landfill leachate[135] and wastewater[286] treatment facilities if effluents are disinfected by chlorination[233] prior to release.

These disinfection by-products can include mono- and poly-chlorinated forms of **1a** including the tetra-chlorinated **1c**.[134,135] When product mixtures resulting from chlorination of **1a** in water were tested in a binding assay employing a recombinant form of the endogenous human classical oestrogen receptor,[287] ERα, 24-fold greater activity than the untreated **1a** solution was observed.[134] The mixtures also induced β-galactosidase activity in a yeast two-hybrid system employing human ERα.[134] In addition, 2-ClBPA, 2,2′-diClBPA, 2,6-diClBPA, 2,2′,6-triClBPA and **1c** exhibited oestrogenic activity as measured by oestrogen-induced green fluorescent protein expression in transgenic human breast carcinoma MCF7 cells (ERE-GFP-MCF7 cells).[288] In addition to being oestrogenic, the multiply chlorinated forms of **1a** are more resistant to activated sludge treatment than **1a**.[203] Notably, 2,2′-diClBPA only undergoes very slow degradation while 2,2′,6-triClBPA and **1c** are not degraded. Thus, in addition to emissions resulting from the use of **1c** in flame retardants and as an epoxy intermediate,[243] chlorination of **1a**-containing waters may contribute to the **1c** concentrations which have been detected in sewage sludge,[243,289–291] river water[289] and sediment.[289]

Further treatment of WWTP effluent with powdered activated carbon (PAC) or ozone has been advanced to enhance removal of MPs from wastewater.[292] The energy and resource demands of PAC treatment followed by sand filtration (PAC-SF) to retain the PAC and ozone are significant and similar.[293] PAC has been observed to remove 89.5–99% and 33–98.5% of **1a** from pH 8.3 lab and pH 8.3–8.4 raw drinking waters, respectively, and these results are expected to transfer to waters containing ≥500 ng $l^{-1}$ **1a**.[294] However, difficulties arise from handling of the finely powdered PAC and retention of the PAC which can necessitate employment of ultrafiltration membranes at significantly greater cost than either PAC-SF or ozone.[293] Additional problems derive from interference from dissolved organic carbon, a decrease in the performance over time due to saturation and management of the spent PAC, which is expensive to produce for replacement or to regenerate at elevated temperature.[293] BPA is readily degraded by ozone.[295–299] For example, treatment of 10 045 μg $L^{-1}$ **1a** in pH 6.0 lab water with *ca.* 0.1 mg $L^{-1}$ $O_3$ (4.05 mg $O_3$ per min) effects a >98% removal in 10 minutes with *ca.* 20% mineralization.[295] The technical performance of ozone decreases as the water matrix becomes more complex[296] and despite the extensive deployment of ozone in some countries, it is not widely used globally—the reasons vary by country.[88,293] Where it is deployed, staff training, safety measures[293] and additional infrastructure are necessary.

Significant amounts of **1a** have also been detected in recycled cellulose fiber (RCF) plant process solutions, effluents and products, the last of which comprise roughly 50% of the furnish for worldwide paper and board production.[140,202,300] This can result in the previously noted contamination of virgin and RCF products. Thermal receipt papers typically containing low mg $g^{-1}$ quantities of **1a** contribute significantly to RCF contamination.[140] Up to 10% of the thermal paper produced is never used and directly enters recycling streams along with an additional 30% of that which is used.[284] A phase-out of **1a** would remove it from the paper cycle, however a lag period of 10–30 years has been estimated before **1a** concentrations would reach the limit of nondetection.[301] The contamination of RCF with EDs of any description is a wrench in the sustainability machinery required to move the civilization progressively toward renewable feedstocks. For example, incineration of highly **1a**-contaminated waste at state-of-the-art, low-emission facilities has been advanced over recycling as a method for avoiding further contamination of recycled materials.[226] However, incineration precludes the energetic gains and decreased production emissions of material reuse, generates emissions including carbon dioxide[302] and can also generate PCDDs and PCDFs.[104,303,304] Another recently suggested option for dealing with **1a** contamination of feedstocks may involve establishing acceptable levels for **1a** in recycled products.[215] However, any level of **1a** in goods exposes the consumer and compromises material streams. Therefore, improving decontamination methods for removing **1a** from recycling process solutions and waste streams is an important sustainability research trajectory advanced by the empirical results detailed in this study.

Opportunities for **1a** removal vary with whether or not the process includes a deinking stage. In the deinking of paper products, the addition of NaOH, sodium silicate, and surfactants extracts 95% of the contaminating **1a** into the aqueous solution (pH 9.5–11) and sludge.[284,305] The deinking sludge is then separated from the pulp slurry and dewatered. The process water may be clarified prior to reuse resulting in contaminated sludge and the enrichment of **1a** in the process water.[306] Effluents from the pulp thickening process have been reported to contain 196–10 300 μg $L^{-1}$ **1a**.[230] Washing of the pulp also generates contaminated solutions that are reused and may be bleached.[305,306] If alkaline paper recycling plant pulping solutions are chlorine-bleached, chlorinated forms of **1a**, including **1c**, can be generated,[203] as noted above. Primary treatment of these process waters transfers 95.9% of the influent **1a** to the primary sludge.[284] The water is then sent to a WWTP for secondary treatment, often with activated sludge. In a study of 40 Korean WWTPs that receive influent comprised of varied proportions of industrial and domestic effluent, the concentrations of **1a** detected in sludge at plants receiving primarily industrial effluent (I-WWTPs, >70% of inflow rate from industrial wastewater) were an order of magnitude greater than those receiving primarily domestic effluents (D-WWTPs, 0–3% of inflow rate from industrial wastewater).[216] Of the I-WWTPs, the highest sludge concentrations of **1a** were found at plants receiving wastewater from the paper industry.

If deinking is not necessary, such as in the production of corrugated packing materials, the majority of **1a** remains in the finished paper products limiting opportunities for removal and creating sources of environmental contamination. However, 10% of the influent **1a** is transferred to water from the pulping process which is sent to primary treatment where 50% is removed with 18% incorporated into the primary

sludge and 32% unaccounted for.[284] Final effluents have been reported to contain significant quantities of **1a** (Japan 2002: 0.2–370 μg $L^{-1}$, average of 59 μg $L^{-1}$).[230] In most plants, this effluent is subjected to secondary treatment with activated sludge.[306] The deinking, primary, and secondary sludges are dewatered and dried. These are then incinerated with negative to low net energy production, used in biogas production, landfilled, or applied to agricultural land where allowed by law. Thus, the massive global use of BPA in myriad products and processes further burdens an overstrained water treatment infrastructure where upgrading and maintenance require great public expense. Low cost, high efficiency BPA removal approaches, such as the lab experimental results herein promise, can improve both the technical and cost performances of dealing with this contamination.

### TAML/peroxide removal of BPA from water

One green science strategy for reducing exposures to compounds such as **1a** is to pursue safer, more efficient and flexible stewardship processes. To this end we have been developing TAML activators (**2** is the prototype, Fig. 1) which are highly effective catalysts for $H_2O_2$ oxidations. TAML catalysts and TAML/$H_2O_2$ processes appear to be environmentally benign based on a diversity of evidence[307–310] and, as further shown here, are extremely simple to deploy. TAML/$H_2O_2$ processes have been employed to oxidatively destroy numerous targets in water,[311–315] including bromo-,[310] chloro-[309] and nitro-[316] phenols, drugs,[317] thiophosphate pesticides,[318,319] molluscicides,[320,321] nitroaromatics,[316,322] the *B. atrophaeus* non-infectious surrogate for pathogenic *B. anthracis* and protozoa,[323] dyes,[324–327] coloured paper industry effluents,[328] and signature oestrogenic micropollutants.[4,329,330] Importantly, **2**/$H_2O_2$ chemistry is comprised exclusively of biochemically common elements as a foundational strategy for avoiding toxicity.

The destructive potency toward micropollutants[315,331] suggests that **2** should easily oxidise electron rich **1a** and BPA-like compounds. In fact, well over a decade ago at Carnegie Mellon, **1a** was one of the first compounds studied in this context. At that time, **2**/$H_2O_2$ was found to readily catalyse the oxidative elimination of BPA from water.[332] However, further studies revealed a pH-dependence of the product distribution. As detailed herein, at pH > 10 **2**/$H_2O_2$ oxidizes **1a** rapidly and deeply giving a potential solution for BPA water contamination. At or near neutral pH (optimal for most water treatment processes), **2**/$H_2O_2$ induces oligomerisation of **1a** to form precipitates as the principal products. While this could also represent a solution, the toxicity properties of the aqueous products were unknown, and the intervening years of this long study were primarily focused on developing confidence that no new toxicities were being introduced.

This concern is well-grounded in literature precedent. The unanticipated formation of phenolic oligomers found in the demethylation of anethole (Fig. 1) resulted in the discovery of hexestrol (Fig. 1).[94] Hexestrol is a mono-hydrogenated form of diethylstilbestrol (DES, Fig. 1), a compound structurally similar to **1** that, at the time, was one of the most potent known oestrogens with *ca.* one hundred thousand-fold greater oestrogenic activity than **1a** as indicated by the relative minimum total weights of a substance required to induce a full oestrus response in ovariectomized female rats when administered by six injections over three days of a solution in sesame oil.[333,334] Additionally, the oxidation of **1a** by fungal manganese peroxidase[335] has been observed to give a product mixture containing hexestrol. Therefore, in all cases, evidence was clearly needed that the treated solutions do not contain compounds that are also MPs across the domain of endocrine endpoints and beyond. Addressing these concerns necessitated the development of methodologies for analysing the catalysts and post-treatment solutions. In 2008, through the leadership of J. P. Myers and *Advancing Green Chemistry*, a coalition of environmental health scientists and green chemists formed to develop and eventually publish in this journal the Tiered Protocol for Endocrine Disruption (TiPED).[336] The TiPED is an organized suite of mammalian, fish and amphibian, cellular and computational assays designed to detect low dose, adverse effects as a pre-commercial guide to the chemical enterprise for avoiding EDs and MPs. The development of this protocol and the various resulting collaborations,[4,307,308,336] as extended herein, have allowed TAML activators and TAML-treated BPA media to be scrutinized for low dose toxicity.

Herein, we present a study of **2**/$H_2O_2$ treatment of **1a** in lab water at near neutral pH and at pH 11 to determine the potential for improved decontamination of **1a**-containing waters. This work demonstrates the many levels of complexity that accompany the oxidative degradation of BPA and its derivatives in water treatment. Here we report (i) that **1a–d** are all readily decomposed by **2**/$H_2O_2$ at pH 11 and substantially mineralized and effectively eliminated from water, (ii) that **2**/$H_2O_2$ treatment of high concentrations of **1a** at near neutral pH leads to a green procedure for oligomerising BPA, (iii) on the acid–base and redox properties of **1**, (iv) on an improved synthesis of **12** (Scheme 4), a product of enzymatic degradation of BPA, (v) on a kinetic and mechanistic study of the oxidation of **1a–d** and, (vi) on the toxicity of **1a** samples before and after **2**/$H_2O_2$ treatment at pHs 8 and 11 *via* bacterial, oestrogenicity, and zebrafish developmental assays. Given that **1a** and **1d** are deployed commercially in large quantities, the work also highlights the requirement for further investigation of the degradation profiles of **1b–d** and points to the need for expanded studies on the environmental safety of the **1a–d** oligomers.

## Experimental section

### Materials

Bisphenol A (**1a**, Sigma Aldrich, GC grade >99%) was purified by re-crystallization using a mixture of hot ethanol and water and **2** was obtained from GreenOx Catalysts, Inc. Fresh stock solutions of $H_2O_2$ were prepared daily from reagent grade $H_2O_2$ (30% w/w, Fluka) and standardized by measuring the absorbance at 230 nm ($\varepsilon$ = 72.8 $M^{-1}$ $cm^{-1}$).[337] All other chemicals and solvents obtained from Sigma-Aldrich or Fischer Chemicals were of ACS reagent grade quality or higher and

were used as received. Water was either Fisher HPLC grade or deionized Milli-Q water (Millipore). Regenerated Cellulose (RC) 15 mm syringe filters (0.2 μm pore diameter) were supplied by Phenomenex.

### Synthesis of 4-(4-(4-hydroxyphenyl)-2-methylpent-4-en-2-yl)-phenol, a precursor of 12 (Scheme 4)

Bisphenol A (15.2 g, 0.07 mol) was dissolved in concentrated $H_2SO_4$ (50 mL) and stirred (20 min) at 22 °C. The reaction mixture was quenched by transfer into deionized water (900 mL) in an Erlenmeyer flask with vigorous stirring. The solids were filtered on a medium porosity frit and the filtrate was extracted 3 times with diethyl ether (3 × 200 mL). The organic extracts were washed with aqueous $NaHCO_3$ (5%, 100 mL) and combined with the solids. The resulting solution was dried over $MgSO_4$, filtered, and the solvent was removed by rotary evaporation. The residue was purified by flash chromatography on silica gel with 2 : 1 hexane : ethyl acetate to yield a white solid (3.5 g, 0.01 mol, 15%). $^1$H NMR (300 MHz, $d_6$-acetone, $J$ in Hz) $\delta$ 8.20 (s, 1H, OH), 7.95 (s, 1H, OH), 7.17 (dd, $J$ 8.8, 7.4, 4H, ArH), 6.72 (t, $J$ 8.8, 4H, ArH), 5.04 (d, $J$ 2.2, 1H, =CH), 4.68–4.66 (m, 1H, =CH), 2.75 (d, $J$ 0.8, 2H, $CH_2$), 1.16 (s, 9H, $CH_3$). ESI-MS ($m/z$, negative mode): 267.3 (100), 268.2 (17), 269.2 (3%).

### Synthesis of 4-(prop-1-en-2-yl)phenol (12) (Scheme 4)

4-(4-(4-Hydroxyphenyl)-2-methylpent-4-en-2-yl)phenol (3.5 g, 0.01 mol) and NaOH (9 mg) were placed in a vacuum distillation apparatus to which a water aspirator was connected. The product was distilled under vacuum at 200 °C using a silicone oil bath and a fraction boiling in the range of 75–135 °C was collected. The light-yellow solid was dissolved in diethyl ether (5 mL) and was added to deionized water (25 mL). The mixture was stirred rapidly and sparged with nitrogen until a white precipitate was observed. This was isolated by suction filtration on a fine porosity glass frit (2.3 g, 0.020 mol, 86%). An analytical sample was recrystallized by slow evaporation of diethyl ether from heptane. $^1$H NMR (300 MHz, $d_6$-acetone): $\delta$ 8.20 (s, 1H, OH), 7.36 (d, $J$ 8.9, 2H, ArH), 6.80 (d, $J$ 8.9, 2H, ArH), 5.26 (dq, $J$ 1.6, 0.8, 1H, $H^2$), 4.93 (quintet, $J$ 1.5, 1H, $H^1$), 2.09 (dd, $J$ 1.5, 0.8, 3H, $CH_3$). $^1$H NMR (500 MHz, $H_2O$ + $D_2O$) $\delta$ 7.41 (d, $J$ 8.8, ArH), 6.67 (d, $J$ 8.8, ArH), 2.11 (s, $CH_3$). $^1$H NMR (500 MHz, $H_2O$ + $D_2O$) $\delta$ 7.41 (d, $J$ 8.8, ArH), 6.67 (d, $J$ 8.8, ArH), 2.11 (s, $CH_3$). GC-MS ($m/z$): 134 (100), 119 (77), 94 (14), 91 (35), 77 (15%).

### Methods

UV-vis spectra and kinetic data were obtained using a Hewlett Packard 8453 Diode Array spectrophotometer equipped with a thermostatted cell holder and an 8-cell sample positioner. The temperature was maintained at 25 °C using a Thermo digital temperature controller RTE17 with a precision of ±1 °C. Stock solutions of **1** were prepared by dissolving solid ($7.50 \times 10^{-5}$ mol) in water made basic with KOH (5.0 mL). Stock solutions were then diluted with phosphate buffer (usually pH 11). For experiments at pH 8.5, aliquots of BPA stock solutions (10 000 ppm in $CH_3OH$) were added to the required volumes of 0.01 M buffer (sodium carbonate/bicarbonate) to give solutions with final concentrations of 10 ppm BPA. Aliquots of a **2** stock solution (40 μM in deionised $H_2O$) were added to the **1** containing buffer solutions to give the required final concentration (4–40 nM). Differential pulse voltammetry was performed with an Autolab PGSTAT100 potentiostat and GPES 4.9 software. The working electrode was a glassy carbon disk, with a saturated calomel reference electrode and platinum wire counter electrode. HPLC measurements were performed using a Waters® 600 system with 717 autosampler and 2996 photodiode array detector. Separations were carried out on a Varian Microsorb-MV 100-5 C18 (250 × 4.6 mm internal diameter, particle size 5 mm) column. The system at 40 °C was run in isocratic mode with an acetonitrile/water (3/1) mobile phase. HPLC measurements for the determination of $k_{II}$ at pH 11 were performed using a Shimadzu HPLC system with a Shimadzu CMB-20A controller, LC-20AB pump, DGU-20A3 degasser, SPD-M20A diode array detector, RF-20A XS fluorimeter detector, CTO-20A column oven, and SIL-20A HT auto sampler. Separations were performed on a Phenomenex EVO C18 column at 40 °C with a mobile phase of 50% methanol : 50% water. After $H_2O_2$ addition to initiate reactions, aliquots (1 mL) were quenched by addition to an HPLC vial containing a catalase solution—12 000 units of bovine liver catalase or 60 times the concentration capable of destroying 2.0 mL of $H_2O_2$ ($4.0 \times 10^{-3}$ M) in 1 min with shaking (5 min). $^1$H NMR spectra (500 MHz Bruker Avance 500) of the reaction mixtures were recorded for reaction mixtures containing 10% $D_2O$ and **1a** ($1.5 \times 10^{-4}$ M), **2** ($1.5 \times 10^{-7}$ M) and $H_2O_2$ ($7 \times 10^{-3}$ M). The Watergate water suppression technique was applied. Ion chromatography (IC) studies were conducted on a Dionex DX500 chromatography system with a GP50 gradient pump, an AS40 automated sampler, an ED40 electrochemical detector, a LC25 chromatography oven, and an ASRS® 300 (P/N 064554) self-regenerating suppressor. Chromatographic data were analysed using Chromeleon chromatography software (Version 6.70 Build 1820, S/N 50398). IonPac® AS9-HC (4 × 250 mm) analytical and IonPac® AG9-HC (4 × 50 mm) guard columns were obtained from Dionex. The IC analysis was performed under isocratic conditions with an aqueous $Na_2CO_3$ ($9 \times 10^{-3}$ M) mobile phase at a flow rate of 1 mL min$^{-1}$ with the oven temperature set at 35 °C and the SRS current set at 100 mA. The injection volume for all IC samples was 100 μL. The IC mobile phase was prepared with water from a Barnstead Nanopure system. Total organic carbon (TOC) analysis was performed by Analytical Laboratory Services, Inc. Middletown, PA—samples consisted of **1a** treated with **2**/$H_2O_2$ for a 15 min at pH 11.

### Catalytic oxidation processes

Studies were performed across the pH range of 7–12: pHs 11 and 8.5 were chosen for **1a** product characterizations and mechanistic investigations. At pH 11, reactions typically employed **1** ($1.50 \times 10^{-4}$ M), $H_2O_2$ ($7.5 \times 10^{-3}$ M) and **2** (1.5 ×

$10^{-7}$ M). An excess (50-fold) of $H_2O_2$ relative to **1** was used (36 eq. $H_2O_2$ are required for mineralization). Reactions were initiated by addition with mixing of the $H_2O_2$ stock solution to a mixture of all other reagents in 0.01 M phosphate buffer in 10.0 mm quartz cells.

For the studies at pH 8.5, the appropriate buffer (250 mL, 0.020 M) and aliquots of the **1a** and **2** solutions were combined in a volumetric flask (500 mL) and the volume was made up to 500 mL with deionized water to give [**1a**] = $43.8 \times 10^{-6}$ M, [**2**] = (4.0–40) $\times 10^{-9}$ M and [buffer] = 0.01 M. In a typical reaction, an aliquot (120 mL) of this medium was added to a conical flask (500 mL) and the reaction was initiated by adding $H_2O_2$ (54 μL of 8.82 M standard) with mixing in a mechanical shaker (IKA KS 260) at 150 rpm for 180 min. Aliquots (2 mL) were withdrawn at appropriate intervals and catalase treated to remove residual peroxide. This medium was then filtered (RC syringe filter) into an HPLC vial (2.0 mL) and analysed by injection (10 μL) into a Shimadzu LC-ESI-MS Model 2020: Phenomenex MAX-RP C12 column (2.0 × 150 mm) at 30 °C with a mobile phase of 80% acetonitrile/methanol (2/3 v/v) and 20% deionized water pumping at 0.2 mL $min^{-1}$. **1a** was monitored at *m*/*z* 227 (peak at 5 min) under isocratic elution (20 min) in the negative ion mode.

Reaction solutions at pH 8.5 were also subjected to solid phase extraction (SPE) using 500 mg hydrophilic-lipophilic balance (HLB) cartridges from Waters Corp. The cartridges were preconditioned with methanol (2 mL) followed by Milli-Q water (2 mL) and the sample was passed through the cartridge at a flow rate of 10.0 mL $min^{-1}$. The SPE cartridges were dried under high vacuum and then eluted with methanol (5.0 mL) at a flow rate of 3 mL $min^{-1}$. The eluent was collected and dried under a gentle stream of nitrogen gas. The residue was dissolved in methanol (2.0 mL) for analysis by high resolution (HR) mass spectrometry (Bruker micro-ToF-QII, Bruker Daltonics, Germany) coupled with a Dionex Ultimate 3000 HPLC with autosampler (Dionex, Germany) following a previously described procedure.[330] Samples were scanned within the range *m*/*z* 50–1500 in both the positive and negative ESI modes. Pure samples of **1a** and **2** were similarly analyzed. Nitrogen dried methanol eluents were also derivatised for GC-MS analysis by treatment with BSTFA + TMCS (150 μL, 2 h, 60 °C). The samples were then dissolved in benzene (350 μL) and injected (1 μL) onto a column (Restek RXi-5 ms, 30 m long, 0.25 mm ID, 0.25 μm) for GC-MS analysis using an Agilent GC 7890A gas chromatogram equipped with an Agilent 5975C inert XL MSD mass spectrometer with a Triple-Axis detector. $^1$H NMR analysis (Bruker AVIII-400 MHz spectrometer) was also carried out using a sample obtained by SPE extraction of a BPA oxidation reaction after the methanol eluent had been evaporated to dryness under a gentle stream of nitrogen and the products redissolved in $CD_3OD$.

### Kinetic measurements

Monitoring of pH 11 processes was performed at the wavelength of maximal absorbance ($\lambda_{max}$) of the corresponding phenol. Initial rates were calculated using the independently measured pH 11 extinction coefficients [$\varepsilon/M^{-1}$ $cm^{-1}$ ($\lambda_{max}$, nm)]; **1a** [$4.3 \times 10^3$ (294)], **1b** [$3.6 \times 10^3$ (294)], **1c** [$9.0 \times 10^3$ (305)], and **1d** [$10.0 \times 10^3$ (310). The data were analysed using Microsoft Excel 2003, UV-Visible ChemStation (Rev. A. 10.01) and Mathematica (version 10.0) software packages. All measurements were performed in triplicate to obtain the mean values and standard deviations.

### Toxicity measurements

**Microtox®.** BPA stock solutions (10–20 g $L^{-1}$ or 44–88 mM **1a** in 0.25 M aqueous NaOH) were used directly after preparation with **2** ($1.5 \times 10^{-5}$ M) and $H_2O_2$ (0.15 M). The reactions were run for 60 min at 25 °C and pH 12. The pH was adjusted to 8 and *Aspergillus Niger* catalase was added to quench residual $H_2O_2$. EM Quant strips were used to verify that all $H_2O_2$ was decomposed. The samples were filtered through 0.45 μm PTFE membranes and then tested for acute toxicity in the *Vibrio fisheri* Microtox® assay by Coastal Bioanalysts, Inc. of Gloucester VA.

**Yeast oestrogen screens (YES).** For oestrogen screening, samples (2.0 mL) were withdrawn at set intervals and assessed after catalase treatment by the four-hour yeast oestrogen screen (YES) bioassay—the procedure for preparing the yeast culture, growth medium and the testing regime has been detailed elsewhere.[338] This method allowed for the screening of multiple samples in a short amount of time without the need for sample preparation.[339] All sample solutions and blanks (without substrate) were evaluated by measuring the hormone-induced chemiluminescent signal on a Xenogen IVIS-200 optical *in vivo* imaging system. The chemiluminescent signals from solutions collected prior to the addition of **2** or $H_2O_2$ were normalized to 100% oestrogenicity, which served as a reference point for subsequent screening tests during the reaction.

**Zebrafish development.** In order to further test the effects of **2**/$H_2O_2$ treatment of BPA on aquatic organisms, we assessed changes in 22 morphological endpoints over the first 5 days of zebrafish development.[340] All appropriate reaction controls were conducted.

## Results and discussion

### Degradation at pH 8.5

At pH 8, no degradation of **1a** was detected over 1 h in the absence of $H_2O_2$, but **1a** is vulnerable to $H_2O_2$ alone (36% degradation in 60 min). At pH 8.5 in the presence of **2** ($2.4 \times 10^{-8}$ M) and $H_2O_2$ ($4.0 \times 10^{-3}$ M), the concentration of **1a** ($4.38 \times 10^{-5}$ M or 10 000 μg $L^{-1}$) decreased to $3.97 \times 10^{-7}$ M (90 μg $L^{-1}$) within 30 min. Visually obvious differences were found between **2**/$H_2O_2$ oxidation of **1a** at pH ≥11 and at pH ≤8.5. At the lower pHs, white precipitates formed.

The oxidation of **1a** was studied using very low concentrations of **2** to achieve gentle oxidising conditions as a way of

gaining insight into the formation of insoluble material by slowing its rates of formation and potential further oxidation. Following **2**/$H_2O_2$ ($4 \times 10^{-9}$ M/$4 \times 10^{-6}$ M) treatment of **1a** ($4.4 \times 10^{-5}$ M) at pH 8.5 (0.01 M carbonate buffer) for 180 min, HR-ESI-MS (negative ion mode) of the SPE collected reaction media (ESI, Fig. S1a‡) showed two major ions. One was attributable to **1a** (*m*/*z* 227.1082 $[M - H]^-$; calcd for $C_{15}H_{15}O_2$ 227.1067) and the other to a dimer of **1a** apparently formed *via* oxidative coupling (*m*/*z* 453.2076 $[2M - H]^-$; calcd for $C_{30}H_{29}O_4$ 453.2060).

To better characterize the dimer, the crude material was TMS-silylated and analysed by GC-MS. Two major ions were observed. The first, at 51.4 min with *m*/*z* 742 $[M]^+$, is consistent with a tetrasilylated dimer (ESI, Fig. S2a‡). This suggests the formation of the C–C coupled product **3** (Fig. 3). The second, at 53.79 min with *m*/*z* 670 $[M]^+$, is consistent with a trisilylated dimer (ESI, Fig. S2b‡) suggesting the formation of the C–O coupled product **4** (Fig. 3). The **3** : **4** ratio of the relative integrals was *ca.* 14 : 1 *i.e.* the C–C coupling is a dominant pathway. Since authentic samples of the silylated dimers were not available, standard response curves were not generated. $^1$H NMR analysis of small amounts of the crude reaction product before silylation gave spectra with poor signal to noise ratios consistent with a similar **3** : **4** ratio. Signals assigned to the proposed C–C coupled product **3** were clearly visible at $\delta$ 6.78 (d, 8.2), 7.05 (dd, 8.2, 2.4), 7.05 (d, 8.6), 6.68 (d, 8.6) and 1.57 (s) (ESI, Fig. S3‡). C–O coupled isomer signals could not be clearly assigned.

The influence of the **2** concentration on **3** and **4** formation was investigated (ESI, Fig. S4‡). The reactions were monitored at set time intervals by low resolution electrospray ionization mass spectrometry (LR-ESI-MS, negative ion, selected ion-monitoring mode (SIM), *m*/*z* 453) without SPE. With 4 nM **2**, the yields of **3** and **4** reached a maximum after 60 min and then declined slightly over the next 120 min. This **2**/$H_2O_2$ oxidative procedure provides a green chemical synthesis for the oligomers. At 8 and 16 nM **2**, approximately the same amounts of **3** and **4** formed more rapidly, but then declined more quickly, ultimately nearing zero.

The fates of **3** and **4** in treatment with **2** (4 and 40 nM) were next investigated under the same general conditions with a reaction volume of 500 mL and SPE product extraction prior to analysis by high resolution electrospray ionization (HR-ESI). The HR-ESI mass spectrum (ESI, Fig. S1b‡) for treatment with 4 nM **2** showed unreacted **1a** (*m*/*z* 227.1120 $[M - H]^-$; calcd for $C_{15}H_{15}O_2$ 227.1067), oxidatively coupled **1a** dimers (*m*/*z* 453.2095 $[2M - H]^-$; calcd for $C_{30}H_{29}O_4$ 453.2060) and trace trimers (*m*/*z* 679.3084 $[3M - H]^-$; calcd for $C_{45}H_{43}O_6$ 679.3054) while that for treatment with 40 nM **2** showed negligible unreacted **1a** and major peaks for the dimers and trimers (*m*/*z* 679.3084 $[3M - H]^-$; calcd for $C_{45}H_{43}O_6$ 679.3054) with much smaller peaks for tetramers (*m*/*z* 905.4111 $[4M - H]^-$; calcd for $C_{60}H_{57}O_8$ 905.4048) and pentamers (*m*/*z* 1131.4995 $[5M - H]^-$; calcd for $C_{75}H_{71}O_{10}$ 1131.5042). Therefore, the extent of **1a** oxidative polymerisation can be controlled by the concentration of **2** (ESI, Fig. S1 and S4‡).

The ability this chemistry provides to easily achieve a greater than >99% removal of **1a** near neutral pH with the generation of a secondary insoluble waste stream which is entirely composed of polymerized BPA promises a very simple technique for removing BPA from near neutral pH waste streams provided other contaminants do not complicate the chemistry.

### Degradation of BPA at pH 11

The pH 11 (0.01 M, phosphate) and 25 °C, **2**/$H_2O_2$ oxidations of **1** were studied by HPLC, total organic carbon (TOC) analysis, $^1$H NMR spectroscopy, and ion chromatography. In the absence of $H_2O_2$, degradation of **1a** over 1 h is negligible at pH 12. At pH 11 in the presence of **2** ($1.5 \times 10^{-7}$ M) and $H_2O_2$ ($7.5 \times 10^{-3}$ M), the concentration of **1a** ($1.5 \times 10^{-4}$ M or 34 244 μg $L^{-1}$) decreased below the HPLC detection limit ($1 \times 10^{-7}$ M or 23 μg $L^{-1}$) within 15 min. This represents a 99.9% removal without the generation of a secondary waste stream that requires additional treatment. No oligomeric degradation products were detected.

To further study the rapid and complete degradation of BPA by **2**/$H_2O_2$ at pH 11, $^1$H NMR was employed. The spectrum of the parent BPA in water is simple allowing straightforward monitoring of the catalysed oxidation (Fig. 2). Although **2** is paramagnetic in the resting state,[341] at 150 nM noticeable line broadening of the signals of **1a** was not observed. The **1a** aliphatic and aromatic resonances reduced quickly and were no longer visible by 7.25 min. Within 2.75 min, the oxidation produced two new singlets at $\delta$ 2.24 and 8.46 which were assigned to acetone and formate, respectively. These assignments were confirmed by spiking with authentic samples. Plots of integral intensity *versus* time (not shown) indicate that the rates of **1a** decay and acetone formation are similar though the acetone product only accounts for 25% of the **1a** aliphatic signals. After 2.75 min, an AA′BB′ pattern appeared ($\delta$ 6.65 and 7.15), as did three higher field ($\delta$ 1.62, 1.53, and 1.52) resonances.

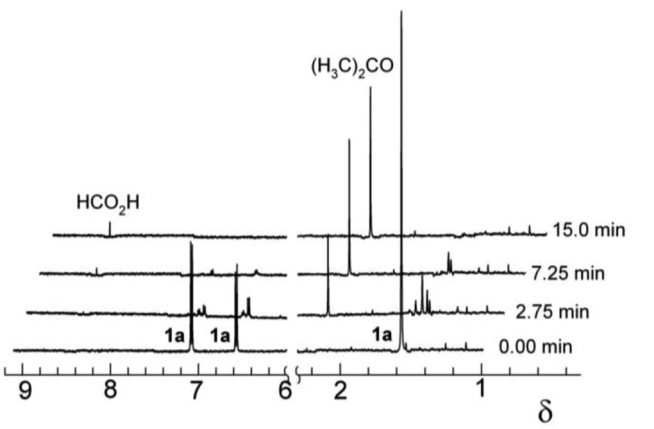



Fig. 2 Progress of the oxidation of **1a** ($1.5 \times 10^{-4}$ M) by $H_2O_2$ ($7 \times 10^{-3}$ M) in the presence of **2** ($1.5 \times 10^{-7}$ M) monitored by 500 MHz $^1$H NMR spectroscopy (Watergate suppression technique). Conditions: pH 11, 0.01 M phosphate, 10% $D_2O$ in $H_2O$, 16 scans per spectrum.

These signals were no longer distinguishable from the baseline at 15 min. At pH 11, the final **2**/$H_2O_2$–**1a** solution was transparent.

As in other TAML degradation studies of phenols and systems with likely phenolic intermediates,[309,318,325,326] ion chromatography (IC) of the final **1b–d** reaction solutions confirms the deep oxidation of **1**. When **1a** ($1.5 \times 10^{-4}$ M) was subjected to **2**/$H_2O_2$ ($1.5 \times 10^{-7}$ M/$7 \times 10^{-3}$ M) for 15 min at pH 11 (0.01 M carbonate), formate (1.7%) was the major observable product by IC. With the more electron-rich and more reactive **1b** (see below for kinetic studies), formate was found at even lower yield (0.7%) under the same conditions. Corresponding 60 min degradations of **1c** and **1d** ([**1**] = $1.5 \times 10^{-4}$ M, [**2**] = $4.5 \times 10^{-7}$ M, [$H_2O_2$] = $7 \times 10^{-3}$ M) liberated 62% of the chloride and 63% of the bromide, respectively.

### Mechanistically relevant acid–base and redox properties of 1

The acid–base properties of **1** are pertinent to the interpretation of kinetic data for the processes described above. Therefore, we have studied the effects of pH on the speciation of **1a** in the range of 8–12 by UV-vis spectroscopy. The data in Fig. 4 show the pH dependence of the UV-spectra. According to the literature, **1a** has a p$K_a$ between 9.59 and 11.30.[91] No well-defined isosbestic points were observed in our UV-vis study, suggesting that both phenolic hydroxides may undergo deprotonation in this pH range. The variation in the absorbance at 295 nm ($A_{295}$) with pH shown in the inset to Fig. 4 could be fit to eqn (1), an analytical form for the dependence of the absorbance on [$H^+$] which corresponds to the deprotonation sequence $AH_2 \rightleftarrows AH^- \rightleftarrows A^{2-}$ ($AH_2$ is **1a**) in which [**1a**]$_t$ is the total concentration of **1a**, $K_{a1}$ and $K_{a2}$ are the first and the second dissociation constants for **1a**, respectively, and $\varepsilon_{AH2}$, $\varepsilon_{AH}$, and $\varepsilon_A$ are the extinction coefficients for the forms $AH_2$, $AH^-$, and $A^{2-}$, respectively. The solid line in the inset is the calculated dependence of the $A_{295}$ on the solution pH using the best-fit values of the parameters of eqn (1). The so-derived p$K_{a1}$ and p$K_{a2}$ of 9.4 ± 0.3 and 10.37 ± 0.07, respectively, indicate that at pH 8.5, the neutral form $H_2A$ is dominant while, at and above pH 11, the dianion $A^{2-}$ is the dominant form of **1a**.

To characterize the relative tendency of substituted phenols **1a–d** to undergo 1-electron oxidation, cyclic and differential pulse voltammetry methods have been applied. As was found previously,[342,343] the **1a–d** reduction potentials could not be determined in aqueous solutions. However, appropriate data could be obtained in acetonitrile *via* application of the differential pulse technique. Examples of the voltammograms are shown as the Inset to Fig. 6 and the corresponding reduction potentials of **1a–d** are included in Table 1. As expected, the electron-donating methyl substituent lowers the reduction potential of **1b** compared to that of **1a**, and **1c** is the most resistant **1** to oxidation.

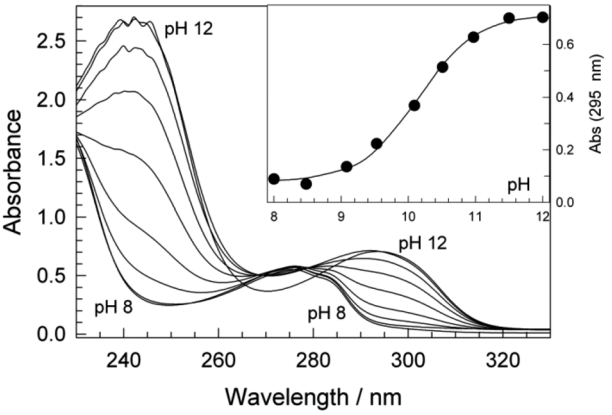



Fig. 4 UV-vis variation with pH for **1a**. Inset shows absorbance changes at 295 nm as a function of pH; the solid line is the calculated dependence using the best-fit values of eqn (1). Conditions: [**1a**] $1.5 \times 10^{-5}$ M, 25 °C, 0.01 M phosphate.

$$\frac{A}{[\mathbf{1a}]_t} = \frac{\varepsilon_{AH2}[H^+]^2 + \varepsilon_{AH}K_{a1}[H^+] + \varepsilon_A K_{a1}K_{a2}}{[H^+]^2 + K_{a1}[H^+] + K_{a1}K_{a2}} \quad (1)$$

### Mechanism of pH 8.5 TAML-catalysed 1a oxidation

Oligomers such as those reported are commonly produced in enzyme-catalysed polymerizations of phenols[347–349] including **1a**.[350–354] The initial step is often proposed to be a one-electron oxidation of the $AH_2$ or $AH^-$ forms of **1a** to produce phenolate radicals which can then couple to give higher molecular weight products.[350–354] Our study mirrors the enzymatic results. There is little doubt that the oxidation starts with 1-electron oxidation of either $AH_2$ or $AH^-$ forms of **1a**. In the former case, deprotonation of the primary radical-cation affords **A** and **B** (Scheme 2), precursors of the coupled C–C and C–O dimers **3** and **4**, respectively (Fig. 3).

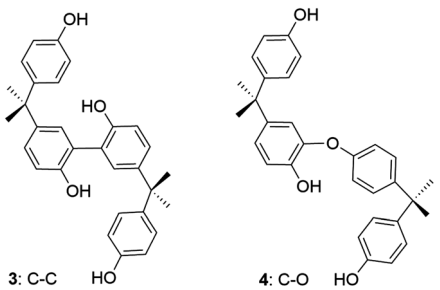
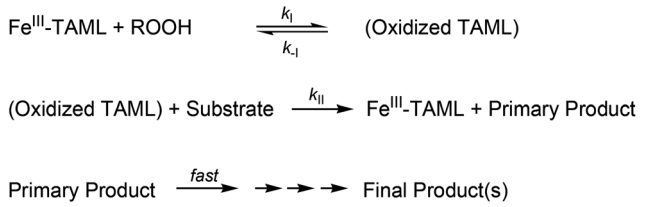



Fig. 3 Proposed coupling products in **2**/$H_2O_2$ oxidation of **1a** at pH 8.5.

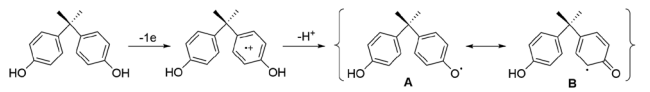
Table 1 Rate constants $k_{II}$ for the interaction of oxidized TAML with **1** (25 °C, pH 11) and the reduction potentials for **1** measured in MeCN (25 °C, $\mu$ = 0.1 M) using differential pulse voltammetry

| **1** (R) | $10^{-4} \times k_{II}/M^{-1}\ s^{-1}$ | $E'$/V (*vs.* SCE) |
|---|---|---|
| **1b** (Me) | 8 ± 3 | 0.181 ± 0.005 |
| **1a** (H) | 1.0 ± 0.4 | 0.26 ± 0.01 |
| **1d** (Br) | 0.72 ± 0.04 | 0.37 ± 0.01 |
| **1c** (Cl) | 0.57 ± 0.08 | 0.41 ± 0.01 |




**Scheme 1** Stoichiometric mechanism of catalysis by TAML/peroxide.




**Scheme 2** Initial steps of **2**/$H_2O_2$ oxidative degradation of **1a** at pH 8.5.

### Kinetic studies of pH 11, 2/$H_2O_2$ oxidation of 1a–d

TAML-catalysis of substrate (S) oxidations by peroxide usually follows the stoichiometric mechanism shown in Scheme 1. The initial rates of substrate oxidation ($v$) are well-modelled by eqn (2), the corresponding rate expression in which $[Fe]_t$ is the total initial concentration of all catalyst species.[314]

$$v = \frac{k_I k_{II}[H_2O_2][S]}{k_{-I} + k_I[H_2O_2] + k_{II}[S]}[Fe]_t \quad (2)$$

Obtaining the rate constants $k_{II}$ for oxidation of **1a–d** by the initial rates method promised to deliver insight into the nature of the degradation process. As with many artificial peroxidase mimics,[314] the step associated with $k_I$ is slow requiring that, when possible, the reaction conditions should be set to ensure that steady-state measurements allow for the determination of $k_{II}$. For TAML **2** such conditions are favoured by high $[H_2O_2]$ and basic pH around 11, where $k_I[H_2O_2] \gg k_{II}[S]$ usually applies and $k_{-I}$ can be assumed to be negligible.[325,344] Under these conditions, eqn (2) simplifies to $v = k_{II}[S][Fe]_t$. Correspondingly, the initial rate is (i) independent of $[H_2O_2]$ in the range of (0.35–1.40) × $10^{-2}$ M, (ii) proportional to the initial concentration of catalyst, [**2**], in the range of (0.375–1.50) × $10^{-7}$ M and, (iii) directly proportional to the concentration of substrate, [**1a**] (Fig. 5).

Similar kinetic measurements were performed for **1c–d** and the second-order rate constants $k_{II}$ were determined from the slopes of the linear plots for **1a**, **1c** and **1d** (Fig. 5, Table 1). The oxidation of methyl-substituted **1b** was considerably faster than all other cases and the initial rate showed saturation with increasing [**1b**], suggesting a contribution of the $k_I$ pathway to the overall rate. Therefore, the data were fitted to eqn (2) (assuming $k_{-I} \sim 0$) and the value of the thus calculated $k_{II}$ appears in Table 1.

We have developed a mathematical tool for modelling TAML catalysis[345] which we have used to examine the comparative behaviour of 15 different catalysts in the oxidation of one substrate under one set of conditions[327] and, more recently, the oxidation of 5 different substrates by 2 different catalysts and 2 different oxidants at two different pHs.[321] We used the $k_{II}$ value for 2/$H_2O_2$ oxidation of **1a** and the **2** $k_i$ value of (7.7 ± 0.3) × $10^{-5}$ $s^{-1}$ determined in 2/$H_2O_2$ oxidation of the azo dye Orange II at pH 11 and 25 °C,[346] to estimate the percent removal of **1a** by 150 nM **2** treatment. The predicted removal of *ca.* 100% agrees well with the observed removal of 99.9% providing further validation of the mathematical model.

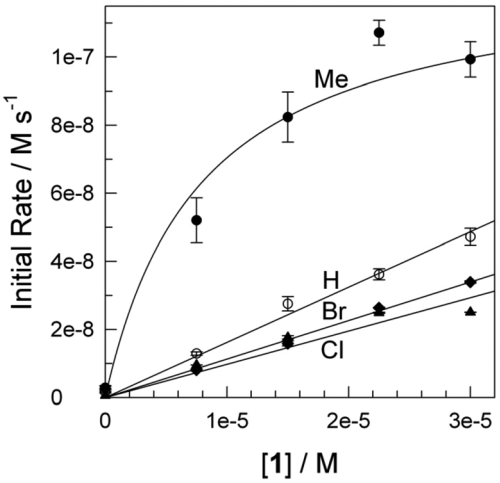



**Fig. 5** Dependence of the initial rate of oxidation of substituted Bisphenol A derivatives **1a–d** (**1**: **a** = H, **b** = Me, **c** = Cl, **d** = Br) by $H_2O_2$ (7.5 × $10^{-3}$ M) catalysed by **2** (1.5 × $10^{-7}$ M). Conditions: 0.01 M phosphate ($Na_2HPO_4$), pH 11, 25 °C.

The **1a–d** phenols were characterized electrochemically to examine if rate-limiting electron transfer is the initial event upon encounter of these electron-rich substrates with the powerfully oxidizing TAML reactive intermediate. The negative slope found for the linear relationship between the values of log $k_{II}$ and the reduction potentials $E'$ (Fig. 6) supports this assignment of the initial step. This correlation and the obser-

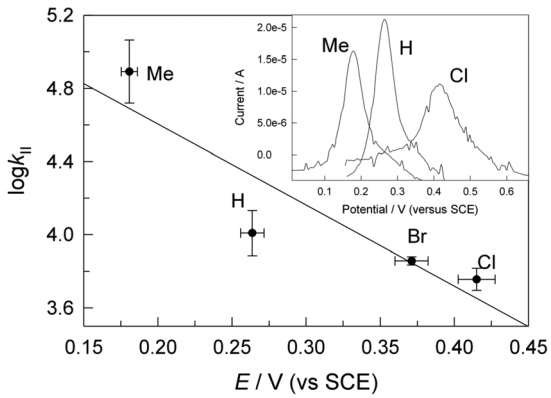


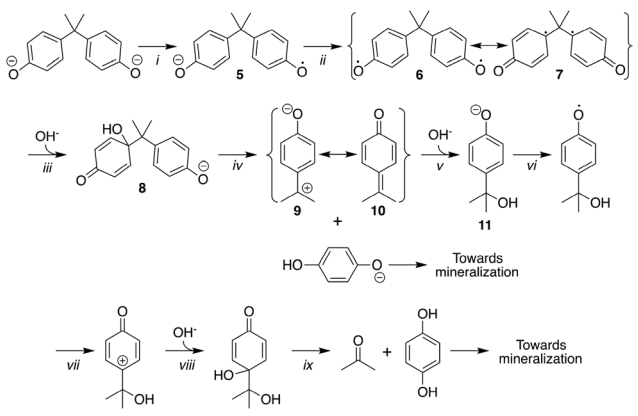

**Fig. 6** Relationship between log $k_{II}$ and experimentally determined reduction potentials of **1** obtained by differential pulse voltammetry in acetonitrile (Inset) of solutions of **1** ([**1**] ≈ $10^{-3}$ M). Conditions: 0.1 M [*n*-$Bu_4N$]$PF_6$ as supporting electrolyte, modulation time 0.05 s, interval time 0.1 s, step potential 0.002 V, modulation amplitude 0.005 V, scan rate 0.1 V $s^{-1}$, glassy carbon electrode.

vation of acetone as a final **1a** degradation product are consistent with the proposed mechanism (Scheme 3).

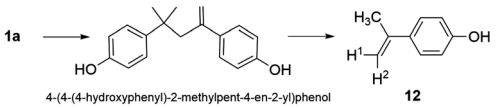
### Tentative mechanism of pH 11 TAML-catalysed 1 oxidation

Since the $pK_{a2}$ of **1a** (10.37 ± 0.07) indicates that the doubly deprotonated $A^{2-}$ form dominates the speciation of **1** at pH 11, and the $k_{II}$ values in Table 1 correlate with the reduction potentials (Fig. 6), and the observed removal agrees well with the removal predicted by the aforementioned mathematical tool, the initial step of pH 11, **2** catalysed **1** oxidation likely involves rate-limiting electron-transfer from $A^{2-}$ to the Oxidized TAML species (Scheme 1) to give the primary product **5** (Scheme 3, step i). Oxidation of the second phenolate would give a compound **6** having resonance form **7** (Scheme 3, step ii).[355] Nucleophilic attack of hydroxide and intramolecular electron transfer would give **8** (step iii), an intermediate proposed in degradation of **1a** by *Sphingomonas* sp. Strain TTNP3 *via* a type II *ipso* substitution mechanism thought to be enacted by a monooxygenase enzyme.[356] Intermediate **8** can undergo heterolysis to give *p*-hydroquinone and the compound represented by resonance structures **9** and **10** [356] where the aromatization provides an important component of the driving force (step iv). The absence of *p*-hydroquinone in the $^1$H NMR spectra of the reaction mixture (Fig. 2) should not be interpreted as an indication that it is not generated. Molecules like *p*-hydroquinone are known to undergo fast oxidation by $H_2O_2$ under similar reaction conditions without involvement of TAMLs.[325]

Since, an intermediate having an AA′BB′ spin system was observed at $\delta$ 6.65 and 7.15 (Fig. 2, 7.25 min spectrum) and 4-(2-hydroxypropan-2-yl)phenolate (Scheme 3, **11**), 4-(prop-1-en-2-yl)phenol (Scheme 4, **12**), a tautomer of **10**, and *p*-isopropylphenol, the reduction product of **12**, have been observed in the product mixtures of bacterial,[357] enzymatic[6,75,335,350,358] thermal,[276–279,359] and/or chemical degradations of **1a**,[360] including that of TTNP3,[356] and the reaction was performed at basic pH, these compounds were investigated as candidates for the reaction intermediate. $^1$H NMR spectra of *p*-isopropyl-




**Scheme 3** Tentative mechanism for **2**/$H_2O_2$ oxidative degradation of **1a** at pH 11 consistent with results and working assumptions derived in this work.




**Scheme 4** Synthesis of **12** from **1a** *via* the intermediacy of 4-(4-(4-hydroxyphenyl)-2-methylpent-4-en-2-yl)phenol (see Experimental section).

phenol and **12**, which was generated from **1a** as reported (Scheme 4),[361,362] obtained under the reaction conditions showed AA′BB′ spin systems at $\delta$ 6.56 and 7.02 and $\delta$ 6.67 and 7.41, respectively, indicating that neither compound accumulated measurably during **2**-catalysed oxidation of **1a**. $^1$H NMR spectra of the crude products of the alkylation of *p*-hydroxyacetophenone with methylmagnesium bromide[363] showed **11**, the presence of which was further confirmed by ESI-MS. However, difficulties were encountered in the isolation of **11**, as has been reported.[363] As a result, we tentatively propose the intermediate to be 4-(2-hydroxypropan-2-yl)phenolate (Scheme 3, **11**), the **1a** analogue of a product observed in **1d** oxidation by $H_2O_2$ catalysed by **2** immobilized in a layered double hydroxide composite.[310] **11** can undergo two successive one electron oxidations, nucleophilic attack of hydroxide and heterolysis with proton transfer (Scheme 3, steps vi, vii, viii and ix, respectively) to give the observed acetone (Fig. 2) and *p*-hydroquinone which would undergo rapid catalysed or uncatalysed degradation.

The material in the above Experimental section promises that, subject to successful real-world testing, a simple to deploy, technically effective, cheap to install and operate TAML/$H_2O_2$ process for removing **1** compounds from water is achievable. The literature covered in the first mini-review establishes ubiquitous **1a** occurrences in products and water with broad exposures to humans and wildlife. In the following mini-review, we examine the literature describing the consequences of these exposures to underscore the importance of developing more effective treatment processes that, before deployment, are cleared of low-dose adverse effects.

### Mini-review of BPA toxicity

Several derivatives of (4,4′)-dihydroxy-diphenyl methane, which differ in the alkyl substituents of the aliphatic carbon atom, including **1a**, are oestrogens as was briefly communicated in 1936,[23] more thoroughly reported in 1938,[364] 1940 [333] and 1944 [334] and reviewed in 1945.[94] Given this history, it is not surprising that global **1a** contamination can impact exposed organisms.[1,74,75,128,218,219,365] In a 2008 report to the Canadian Government, authors concluded that, "Bisphenol A is acutely toxic to aquatic organisms and is a known endocrine disruptor"[217] which, in 2010, led the Canadian Government to declare **1a** to be toxic and add it to the List of Toxic Substances in Schedule 1 under section 64 of its Environmental Protection Act of 1999.[421]

In adult fish of many species, lab tests show that exposure to the levels of **1a** found in surface waters (earlier mini-review) causes alteration of gene expression including stimulation of

vitellogenin synthesis (a protein that is a precursor of egg yolk protein and a biomarker for exposure to oestrogens) in males, alteration of reproductive traits including reductions in male sperm quality, and delayed or no ovulation in females.[74,366–372] In the embryonic and early life stages of fish development, such exposures have been observed to result in alteration of gene expression, reduction of heart rate, decreased eye pigmentation density, accelerated development, delayed hatching of embryos, testis-ova in males, hyperactivity in larva, and learning deficits in adult males.[373–379]

In addition to these impacts on the exposed fish, lab exposures at typical **1a** surface water concentrations can cause effects in offspring not observed in the parental generation.[365] These multigenerational effects can derive from both adult and developmental exposure to EDs and are measured by assessing the impacts of exposure on members of the initial population (F0) and each subsequent generation (F*n*) *versus* unexposed controls (B0–B*n*).[77,96,380–382] One such study followed the effects of zebrafish exposure to 0.228 μg $L^{-1}$ **1a** on the F0, F1, and F2 generations.[365] In the continuously exposed F1 and F2 generations, decreased male/female sex ratios in the adult population were observed together with lowering of male sperm density and quality including decreased motility and ATP production as well as increased sperm lipid peroxidation. The majority of the F1 adverse effects on sperm quantity and quality were not found in F2 male offspring if, subsequent to the **1a** exposure, the F1 generation was incubated for 150 days in water to which **1a** was not added, highlighting that these effects may be reduced through reduction of **1a** exposure—the decreased sperm ATP production persisted in F2 males. Increases in malformation and mortality at 8 days post fertilization in the F2 offspring of F1 males indicated male-mediated reproductive failures deriving from **1a** exposure. In the gonads of F2 males, altered gene expression was observed leading to perturbations of signaling pathways including those regulating mitochondrial biogenesis and testis development. In the larvae of F2 parents, reduction in expression of DNA methyl transferases and the associated transcription factor was observed indicating that continuous **1a** exposure can lead to alterations of the epigenome and may result in transgenerational effects such as the observed male specific reproductive failures.[365]

A US National Institute for Environmental Health and Safety panel has concluded that the available laboratory rodent studies provide sufficient evidence to be "confident" of human effects including effects on the male reproductive tract arising from adult exposures and effects on the organization of the reproductive tract of males, the brain and metabolism arising from developmental exposures.[92] A US National Toxicology Program panel[383] and the US Food and Drug Administration[79] also concluded that there is "some concern" for effects on the brain, behavior, and prostate gland in foetuses, infants and children arising from exposure to **1a** at levels currently observed in the human population (earlier mini-review). However, further studies accounting for contributions to human **1a** exposure from dermal absorption and of the toxicokinetics following dermal absorption need to be performed.[85] We proceed by highlighting laboratory studies that reflect the human effects of **1a** exposure to the concentrations found in foetal, child and adult fluids and tissues (0.3–4.4 μg $L^{-1}$ or 1.3–19 nM).[120] Reviews of the epidemiological studies[384–388] on the effects of human **1a** exposure not discussed herein are available.[68,389]

Exposure to **1a** at and slightly below the concentrations found in foetal, child and adult fluids and tissues can alter cellular development and produce mature cells which are improperly programmed. For example, exposure of HL-60 leukocytes to 1 nM **1a** during neutrophilic differentiation induced by 1.25% dimethylsulfoxide and 25 ng $mL^{-1}$ granulocyte colony-stimulating factor results in significant increases in PU.1 transcription factor activity and production of opsonized zymosan (OZ) receptor subunit CD18 and $O_2^-$ stimulating NADPH-oxidase components p47phox and p67phox mRNA during differentiation *via* an oestrogen receptor independent mechanism, as well as differentiated cells with increased CD18 expression on the cell surface and OZ-stimulated $O_2^-$ production suggesting that long-term **1a** exposure may significantly affect human immunity.[390]

Exposure of day 7 human prostaspheres, prostate stem-progenitor cells, to **1a** at human relevant concentrations resulted in rapid membrane-initiated oestrogen signalling with increased levels of p-Akt and p-Erk, downstream targets of membrane ERs, and Erk phosphorylation, which were sustained for at least 60 minutes and returned to baseline by 6 hours, a result similar to that obtained from exposure to the same concentration of E2, an endogenous hormone.[391] Further insights into the effects of **1a** exposure on prostate development have been gained through application of an *in vivo* renal graft model of chimeric human-rat prostate tissues. This model employs mice which express human prostate epithelial stem-progenitor cells that form normal human prostate epithelium, which produces prostate-specific antigen.[392] Treatment of the host mice with testosterone and E2 for 1–4 months to model the elevated E2 levels of later life-staged men increases the transition of the human prostate cells from hyperplasia to prostatic intraepithelial neoplasia and adenocarcinoma demonstrating the role of E2 in cancer of the human prostate epithelium.[391] Oral exposure of the host mice to **1a** dosages giving free **1a** serum levels of 0.39 and 1.35 μg $L^{-1}$, comparable to the internal doses found in human umbilical cord blood and foetal and neonatal serum, for 2 weeks after renal grafting resulted in mice having reduced normal prostate incidences from the control 26% to 11 and 0%, respectively, increased benign lesion incidence from the control 74% to 89 and 100%, respectively, and increased malignant lesion incidence from the control 13% to 36 and 33%, respectively, upon initiation/promotion of hormonal carcinogenesis by administration of testosterone and E2 for 2–4 months.[391] If, to model continuous exposure throughout development, prostaspheres were exposed to **1a** *in vitro* prior to *in vivo* exposure, incidences of malignant lesions further increased to 45%. These results indicate that exposure of

developing human prostate epithelium to doses of **1a** relevant to those observed in human development increases its susceptibility to hormonal carcinogenesis.[391]

Exposure to **1a** at and slightly below the average concentrations found in human blood also alters the functioning of developed cells. For example, exposure of developed human pancreatic β-cells to 1 nM **1a** in the absence of glucose rapidly decreased the activity of $K_{ATP}$ channels as effectively as exposure to 8 mM glucose, and in the presence of a stimulatory concentration of glucose (8 mM), exposure of human pancreatic islets of Langerhans to 1 nM **1a** enhanced insulin secretion *ca.* 2 fold demonstrating that **1a** exposure may be a risk for the development of type-2 diabetes.[393] Exposure of human breast, subcutaneous and visceral adipose tissue explants and mature adipocytes to 1 and 10 nM **1a** suppressed the release of adiponectin, an insulin sensitizer, a result similar to exposure to equimolar concentrations of E2.[83,394] Exposure of human adipose explants to 10 nM **1a** stimulated the release of inflammatory cytokines IL-6 and TNFα which promote insulin resistance. Taken together, the adipose tissue and adipocyte results indicate that exposure to **1a** at population relevant levels may adversely effect metabolic homeostasis.[83,394]

Exposure to **1a** at and slightly below the average concentrations found in human blood and serum also alters the behaviour of cancer cells in tumours. For example, exposure of human androgen-dependent prostatic adenocarcinoma cells, a model system for prostate tumours, to 1 nM **1a** has been observed to activate AR-T887A leading to androgen independent cellular proliferation like that resulting from exposure to 0.1 nM dihydrotestosterone, an endogenous ligand, though **1a** activation may occur indirectly through interaction with ERβ or other proteins.[395] This result indicates that **1a** exposure may ease the transition of prostatic adenocarcinomas to androgen independence,[395] thereby challenging treatment.[84] Exposure of both wild-type MCF7 breast cancer cells and an MCF7 subline, MCF7SH, which models the behaviour of long-term oestrogen deprived breast tumor cells, to 10 nM **1a** has been observed to stimulate cellular growth, a response similar to, but weaker than that observed upon exposure to 10 nM E2, and this behaviour has been attributed to classical genomic activation of ERα.[191]

While the observation of weaker response to **1a** than E2 would seem to reflect a general, lower potency of **1a**, as would be anticipated to result from the known, weaker binding of **1a** to classical oestrogen receptors, this is not always the case. For example, *in vitro* exposure of MCF-7 cells, which express both ERα and ERβ, MDA-MB-231 cells, which express ERβ only, and SKBR-3 cells, which express neither ERα nor ERβ to 0.1–100 nM **1a** in the presence of 2 mM $Ca^{2+}$ results in rapid $Ca^{2+}$ influxes in all three cell types leading to increases in intracellular calcium concentrations ($[Ca^{2+}]_i$) comparable to those resulting from exposure to equimolar concentrations of E2.[22] These results implicate **1a** in non-genomic signalling pathways, such as membrane ERα (mERα) initiated signalling, and agree with those from *in vitro* studies employing rat pituitary tumor cell sublines GH3/B6/F10 (F10), which naturally expresses high levels of mERα, and GH3/B6/D9 (D9), which naturally expresses low levels of mERα. *In vitro* exposure of F10 cells to either 1 pM E2 [21] or 1 pM **1a** [20] results in rapid and reversible influx of extracellular $Ca^{2+}$ leading to nearly equal increases in $[Ca^{2+}]_i$, which results in prolactin secretion and can initiate signaling cascades that lead to changes in cellular protein phosphorylation that alter protein functioning. Exposure of D9 cells to either 1 pM E2 [21] or 1 pM **1a** [20] does not alter the $[Ca^{2+}]_i$. Thus, **1a** can be as potent as E2 in eliciting responses mediated by non-genomic pathways reinforcing that it is inappropriate to label **1a** a weak oestrogen.[20,22,393]

Similar potency of BPA and EE2 has also been observed *in vivo*.[396] This may result from the formation of a BPA metabolite that either syngergizes[397] with BPA[396] or is significantly more oestrogenic.[17,396,398] One BPA metabolite produced by human liver S9 fractions in the presence of an NADPH-generating system is 4-methyl-2,4-bis(4-hydroxyphenyl)pent-1-ene (MBP, Fig. 1).[17] MBP has several- to several thousand-fold increased oestrogenicity in cellular assays employing ERα and ERβ.[17] One such assay showed MBP to be as oestrogenic as diethystilbestrol (DES, Fig. 1),[17] prenatal exposure to which is known to increase the risk of breast[42] and vaginal[399] cancers.[105] An *in vivo* uterotrophic assay using ovariectomized rats has shown MBP to be *ca.* 500 times more oestrogenic than BPA.[400] The MBP oestrogenicity increase is thought to derive from the increased distance between the phenolic rings which resembles that of benzestrol (Fig. 1),[401] a known oestrogen.[28,402] Studies have also shown MBP to adopt a coplanar conformation like E2 with a similar inter-hydroxyl distance.[17] Therefore, the effects of metabolites like MBP may contribute to the negative environmental[403,404] and human health[405] impacts of BPA, particularly if glucuronidation, the predominant, human, **1a** metabolic pathway,[14,15] which gives a monoglucuronide showing almost no oestrogenic activity,[16] does not occur.[17,18] Thus, BPA exposure of foetuses,[68,120,406–410] which are largely incapable of glucuronidation,[19,68,411–414] is particularly concerning and disruption of human development[415] is a potential health impact of BPA and BPA metabolite exposure.[398] This is especially troubling given the known effects of BPA on cellular programming which can increase susceptibility of some organs, including the prostate[391,392,416] and mammary glands[417,418] to the development of cancer.[105,120] Since cytochrome p450 (CYP) operates in the liver fraction S9 metabolism that gives MBP[17,18] and CYP isoforms are expressed in the human foetal liver,[419] *in vivo* foetal BPA exposure may also result in foetal MBP exposure.[17] Unquestionably, the study of endocrine disruption phenomena associated with BPA metabolites should be a future research priority as there is enough already known to suggest that an under-recognized potent toxicity might be impacting human foetal development.

Along with numerous others, these studies of the effects of exposure to **1a** on embryonic, early life stage and adult fish of many species and the zebrafish epigenome at environmentally relevant concentrations and of the effects of exposure to **1a** on

developing, developed, and cancer cells at concentrations relevant to those observed in the human population reinforce that **1a** is an endocrine disruptor with negative environmental and health performances to challenge the on-going viability of many current applications.[12,86,217,420]

With these studies providing a useful background we now describe the toxicity assays used to examine the TAML/$H_2O_2$ **1a** treatments described in this work.

### Toxicity of the treated 1a solutions

One-hour reaction mixtures (Table 2) were adjusted to neutral pH, quenched with catalase, and tested for acute toxicity using the Microtox assay.[422] Samples obtained at pH 8, where solids form in the dominating oligomerization of this pH region, were filtered before the assay. Although the oligomers are insoluble, we emphasize that these species are important aspects of the environmental profile of pH 7 treatments. A thorough exploration of the endocrine activity of the water insoluble oligomers is beyond the scope of the current study—if precipitation occurs in real-world media this would be an excellent way to isolate waste **1a** in a form having diminished potential for long range transport. The results (Table 2) show that samples treated with $H_2O_2$ in the presence of **2** were less toxic than those treated with $H_2O_2$ alone. An $EC_{50}$ of >100% indicates that the undiluted sample was not toxic enough to affect 50% of the organisms. At pH 8, only 5 molar equivalents of $H_2O_2$ were necessary to effect this reduction in toxicity. At pH 12, the $H_2O_2$ requirement increased to 50 molar equivalents.

Solution concentrations of **1a** can be lowered to nearly zero by polymerizing treatment at pH 8.5 (Fig. 7a). It is prudent to show that these oxidised products, though effectively isolated, do not themselves have oestrogenic activity. This important point was illustrated by a recent study in which it was demonstrated that removal of EE2 from solution through partial oxidation produced soluble products that have similar oestrogenic activity as EE2 itself.[330] Therefore, the oestrogenic activities of the **1a** solutions were evaluated by the yeast oestrogen screen (YES)[339] after oxidation with **2** at concentrations of 4, 16, 24 and 40 nM at time 0 and after 10 and 60 minute reaction times. The results are depicted in Fig. 7b. In all cases the oestrogenic activity was reduced, with the higher catalyst levels producing faster and more significant drops in activity. After 60 min, the solutions resulting from the reactions with **2** concentrations of 16, 24 and 40 nM showed almost no residual oestrogenic activity while the solutions resulting from reaction with 4 nM **2** showed approximately 75%. In all cases the residual oestrogenic activity correlated well with the amount of **1a** remaining in solution. Therefore, it appears that the product solutions of oxidised **1a** have no activity, and the **1a** remaining can serve as an indication of the residual oestrogenicity of the treated solution.

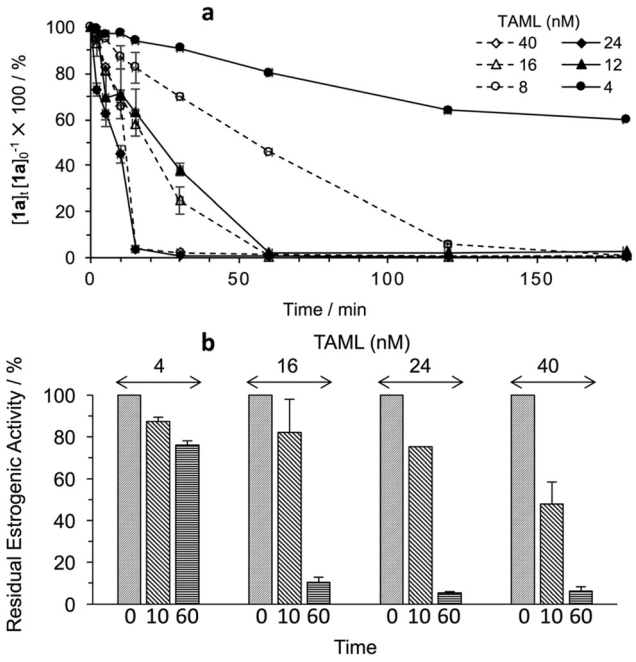



**Fig. 7** (a) Kinetic traces of **2** (concentrations shown) catalysed oxidation of **1a** (43.8 μM) by $H_2O_2$ (4 mM) at pH 8.5 (0.01 M, carbonate) and 25 °C. Data points are each the mean of triplicate runs with estimated 3SD limits indicated. (b) Residual oestrogenic activity as a function of treatment time for some of the processes shown in (a).

**Table 2** Acute toxicity (Microtox test) of **1a**, **1a** + $H_2O_2$, and **1a** + $H_2O_2$ + **2**-treated samples. Conditions: $5 \times 10^{-3}$ M **1a**, $5 \times 10^{-6}$ M **2**, pH 12

| Reaction pH | $H_2O_2$ (equiv.) | $EC_{50}$ (no **2**)/% | $EC_{50}$ (**2**-treated)/% |
|---|---|---|---|
| n/a | 0 | 21.2 ± 1.7 | 24.5 ± 1.3 |
| 8 | 5 | 20.7 ± 1.6 | >100 |
| 12 | 5 | 22.0 ± 0.8 | 38.0 ± 2.6 |
| 12 | 50 | 23.0 ± 0.3 | >100 |

To further test for aquatic toxicity of **2**/$H_2O_2$ treated **1a** solutions, starting at 6 hours post fertilization, dechorionated zebrafish embryos were exposed to solutions containing 0.01 to 1% of the treated samples. This was done twice. In the first test, 50 μM **1a** was treated with **2**/$H_2O_2$ (20 nM/5 mM, respectively) at pH 7 (0.01 M, phosphate) and quenched with catalase at 12 h. From the unfiltered, agitated, treated solution, more dilute solutions (0.2–2 μM, based on the initial concentration of **1a**) were prepared, and the embryos were exposed to the diluted solutions. In the second test, 80 μM **1a** was treated with **2**/$H_2O_2$ (200 nM/5 mM, respectively) at pH 7 (0.01 M, phosphate) and quenched with catalase at 12 h. From the unfiltered, agitated, treated solution, more dilute solutions (0.08–64 μM, based on the initial concentration of **1a**) were prepared, and the embryos were exposed to the diluted solutions. With the treatment conditions chosen, no significant incidences of abnormality among any of the 22 endpoints were observed (ESI, Fig. S5‡). However, an insignificant increase in mortality was observed for the treated samples compared to the untreated samples.

## Conclusion

In developing Green Chemistry, it is important that chemists come to understand the scope of the challenges posed by everyday-everywhere endocrine disruptors (EDs) to the sustainability of both the chemical enterprise and our complex global civilization. The most troubling such EDs, like BPA, invariably hold their protected positions in the economy because of seductive technical and cost performances that enable large, diverse, profitable markets. For sustainable chemicals, the health, environmental and fairness performances also have to be integral components of the value proposition. Understanding the negative performances of unsustainable chemicals helps in mapping the properties sustainable chemicals should not have. Key aspects of this understanding include the knowledge of which chemicals are and are not EDs and are and are not capable of eliciting low dose adverse effects by non-endocrine processes, the extent and routes by which the environment and people are exposed to commercial EDs, the environmental and human health consequences of ED exposures, the methods of assessment of endocrine activity[423] including the TiPED,[336] the mechanisms of the low dose adverse effects, the design approaches to attaining new and replacement chemicals free of such effects,[307] and the stewardship methodologies that are currently deployed or might be deployed to better protect health and the environment from commercial EDs. This BPA case study traverses the appropriate multidisciplinary landscape with emphasis on the integration of chemistry and environmental health science in the development of endocrine disruption-free processes to aid the chemical enterprise and society in reducing BPA exposures. Importantly, the litany of unfortunate facts presented about BPA exposures and health and environmental performances is relieved to some extent by the possibility of reduced releases arising from the TAML/$H_2O_2$ technology mapped out in the empirical section.

This experimental component demonstrates that TAML/$H_2O_2$ provides simple, effective water treatment methodologies, which depending on the pH, either decompose **1a** or isolate it in low solubility oligomers. Both processes require only very low concentrations of **2** and $H_2O_2$ in further reflection of the remarkable efficiencies of the peroxidase enzymes that are faithfully mimicked by **2** and in marked contrast with the much higher relative iron- and peroxide-requiring Fenton processes. It remains to be established whether the current laboratory studies project to real world scenarios. These may include treatment of **1a**-contaminated landfill leachates and paper plant processing solutions where the concentrations are similar to those employed in this study. In such scenarios, TAML/$H_2O_2$ would present an enzyme-mimicking method which in the case of **2** is comprised exclusively of biochemically common elements and has passed multiple TiPED assays that, in contrast with existing real world processes, avoids generation of **1a**-contaminated sludges and associated subsequent releases to soil, that does not generate a **1a**-contaminated adsorbent which must be replaced or regenerated at elevated temperature, that does not generate chlorinated forms of **1a**, that does not generate a concentrated retentate, and that is remarkably simple to deploy using very low and cheap chemical inputs with all the positive potential consequences thereof for capital and operating expenses.

Finally, in order to avoid the habit or perception of greenwashing, a realistic perspective is essential to the integrity of green chemistry. We view the sustainability challenges posed by BPA as enormous—the experimental work presented could evolve into a solution for some of these problems but is, by no means, a general quick fix. BPA markets large and small are expanding rapidly, especially as the industry has learned how to produce even more effective replacements for glass and metal products. Huge new markets are developing such as those of plastic glass houses, and even houses, and automobile body parts that are comprised primarily of BPA. In this build-up, BPA's unfortunate health and environmental performances continue to be given short shrift. Continuation of the present BPA expansion trends without limits, technical corrections and more aggressive stewardship advances of multiple kinds will menace society with an ever increasing oestrogenization of the entire ecosphere.

## Acknowledgements

Y. O. was a University of Auckland Doctoral Scholarship Recipient. E. S. B. was an NSF Predoctoral Fellow. A. D. R. was an Alexander von Humboldt Foundation Fellow during part of this project. M. R. M. was a CMU Steinbrenner Fellow. M. R. M. and S. K. were CMU Presidential Fellows. T. J. C. thanks the Heinz Endowments for funding and the Heinz Family Foundation for the Teresa Heinz Professorship in Green Chemistry. The authors thank Allan Carl Jackson III and Prof. Laura Vandenberg for valuable suggestions and the reviewers—especially the one who suggested splitting the review material into two mini-reviews, which greatly improved the logic and flow of the material presentation. The $^1$H NMR spectrometers of the Department of Chemistry's NMR Facility at Carnegie Mellon University were purchased in part with funds from the National Science Foundation (CHE-0130903).

## Notes and references

1 R. K. Bhandari, S. L. Deem, D. K. Holliday, C. M. Jandegian, C. D. Kassotis, S. C. Nagel, D. E. Tillitt, F. S. vom Saal and C. S. Rosenfeld, *Gen. Comp. Endocrinol.*, 2015, **214**, 195–219.
2 R. K. Bhandari, F. S. vom Saal and D. E. Tillitt, *Sci. Rep.*, 2015, **5**, 9303.
3 R. T. Zoeller, T. R. Brown, L. L. Doan, A. C. Gore, N. E. Skakkebaek, A. M. Soto, T. J. Woodruff and F. S. Vom Saal, *Endocrinology*, 2012, **153**, 4097–4110.

4 M. R. Mills, K. Arias-Salazar, A. Baynes, L. Q. Shen, J. Churchley, N. Beresford, C. Gayathri, R. R. Gil, R. Kanda, S. Jobling and T. J. Collins, *Sci. Rep.*, 2015, **5**, 10511.
5 C. A. Kinney, E. T. Furlong, S. D. Zaugg, M. R. Burkhardt, S. L. Werner, J. D. Cahill and G. R. Jorgensen, *Environ. Sci. Technol.*, 2006, **40**, 7207–7215.
6 Q. Huang and W. J. Weber Jr., *Environ. Sci. Technol.*, 2005, **39**, 6029–6036.
7 Z.-H. Liu, Y. Kanjo and S. Mizutani, *Sci. Total Environ.*, 2009, **407**, 731–748.
8 B. Borrell, *Nature*, 2010, **464**, 1122–1124.
9 *World BPA Production Grew by Over 372,000 Tonnes in 2012*, Merchant Research & Consulting Ltd, 2013, https://mcgroup.co.uk/news/20131108/bpa-production-grew-372000-tonnes.html.
10 Y. B. Wetherill, B. T. Akingbemi, J. Kanno, J. A. McLachlan, A. Nadal, C. Sonnenschein, C. S. Watson, R. T. Zoeller and S. M. Belcher, *Reprod. Toxicol.*, 2007, **24**, 178–198.
11 S. Flint, T. Markle, S. Thompson and E. Wallace, *J. Environ. Manage.*, 2012, **104**, 19–34.
12 S. C. Nagel, F. S. Vom Saal, K. A. Thayer, M. G. Dhar, M. Boechler and W. V. Welshons, *Environ. Health Perspect.*, 1997, **105**, 70–76.
13 W. V. Welshons, S. C. Nagel and F. S. vom Saal, *Endocrinology*, 2006, **147**, s56–s69.
14 W. Völkel, T. Colnot, G. A. Csanády, J. G. Filser and W. Dekant, *Chem. Res. Toxicol.*, 2002, **15**, 1281–1287.
15 J. J. Pritchett, R. K. Kuester and I. G. Sipes, *Drug Metab. Dispos.*, 2002, **30**, 1180–1185.
16 J. B. Matthews, K. Twomey and T. R. Zacharewski, *Chem. Res. Toxicol.*, 2001, **14**, 149–157.
17 S. i. Yoshihara, T. Mizutare, M. Makishima, N. Suzuki, N. Fujimoto, K. Igarashi and S. Ohta, *Toxicol. Sci.*, 2004, **78**, 50–59.
18 K. Okuda, T. Fukuuchi, M. Takiguchi and S. i. Yoshihara, *Drug Metab. Dispos.*, 2011, **39**, 1696–1703.
19 H. Yamada, I. Furuta, E. H. Kato, S. Kataoka, Y. Usuki, G. Kobashi, F. Sata, R. Kishi and S. Fujimoto, *Reprod. Toxicol.*, 2002, **16**, 735–739.
20 A. L. Wozniak, N. N. Bulayeva and C. S. Watson, *Environ. Health Perspect.*, 2005, **113**, 431–439.
21 N. N. Bulayeva, A. Wozniak, L. L. Lash and C. S. Watson, *Am. J. Physiol.: Endocrinol. Metab.*, 2005, **288**, E388–E397.
22 D. E. Walsh, P. Dockery and C. M. Doolan, *Mol. Cell. Endocrinol.*, 2005, **230**, 23–30.
23 E. C. Dodds and W. Lawson, *Nature*, 1936, **137**, 996.
24 N. N. Bulayeva, B. Gametchu and C. S. Watson, *Steroids*, 2004, **69**, 181–192.
25 G. Delbès, C. Levacher and R. Habert, *Reproduction*, 2006, **132**, 527–538.
26 G. S. Prins, L. Huang, L. Birch and Y. Pu, *Ann. N. Y. Acad. Sci.*, 2006, **1089**, 1–13.
27 J. Cross, Z. Werb and S. Fisher, *Science*, 1994, **266**, 1508–1518.
28 J. A. Katzenellenbogen, *J. Med. Chem.*, 2011, **54**, 5271–5282.
29 T. J. Collins, S. W. Gordon-Wylie and C. P. Horwitz, *US Pat.*, 6054580, 2000.
30 B. L. Riggs and L. C. Hartmann, *N. Engl. J. Med.*, 2003, **348**, 618–629.
31 M. L. Stefanick, *Am. J. Med.*, 2005, **118**, 64–73.
32 B. J. A. Furr and V. C. Jordan, *Pharmacol. Ther.*, 1984, **25**, 127–205.
33 M. J. Meyers, J. Sun, K. E. Carlson, G. A. Marriner, B. S. Katzenellenbogen and J. A. Katzenellenbogen, *J. Med. Chem.*, 2001, **44**, 4230–4251.
34 P. Christoforou, P. F. Christopoulos and M. Koutsilieris, *Mol. Med.*, 2014, **20**, 427–434.
35 S. Iwamuro, M. Yamada, M. Kato and S. Kikuyama, *Life Sci.*, 2006, **79**(23), 2165–2171.
36 K. Moriyama, T. Tagami, T. Akamizu, T. Usui, M. Saijo, N. Kanamoto, Y. Hataya, A. Shimatsu, H. Kuzuya and K. Nakao, *J. Clin. Endocrinol. Metab.*, 2002, **87**, 5185–5190.
37 C. Teng, B. Goodwin, K. Shockley, M. Xia, R. Huang, J. Norris, B. A. Merrick, A. M. Jetten, C. P. Austin and R. R. Tice, *Chem.-Biol. Interact.*, 2013, **203**, 556–564.
38 I. Writing Group for the Women's Health Initiative, *J. Am. Med. Assoc.*, 2002, **288**, 321–333.
39 E. E. Hatch, A. L. Herbst, R. N. Hoover, K. L. Noller, E. Adam, R. H. Kaufman, J. R. Palmer, L. Titus-Ernstoff, M. Hyer, P. Hartge and S. J. Robboy, *Cancer, Causes Control*, 2001, **12**, 837–845.
40 F. S. v. Saal, B. G. Timms, M. M. Montano, P. Palanza, K. A. Thayer, S. C. Nagel, M. D. Dhar, V. K. Ganjam, S. Parmigiani and W. V. Welshons, *Proc. Natl. Acad. Sci. U. S. A.*, 1997, **94**, 2056–2061.
41 J. R. Palmer, E. E. Hatch, R. S. Rao, R. H. Kaufman, A. L. Herbst, K. L. Noller, L. Titus-Ernstoff and R. N. Hoover, *Am. J. Epidemiol.*, 2001, **154**, 316–321.
42 J. R. Palmer, L. A. Wise, E. E. Hatch, R. Troisi, L. Titus-Ernstoff, W. Strohsnitter, R. Kaufman, A. L. Herbst, K. L. Noller, M. Hyer and R. N. Hoover, *Cancer Epidemiol., Biomarkers Prev.*, 2006, **15**, 1509–1514.
43 A. Derfoul, F. J. Lin, E. M. Awumey, T. Kolodzeski, D. J. Hall and R. S. Tuan, *J. Cell. Biochem.*, 2003, **89**, 755–770.
44 R. R. Newbold, E. Padilla-Banks and W. N. Jefferson, *Endocrinology*, 2006, **147**, s11–s17.
45 Chemical Bisphenol A (BPA), Classified As Toxic, http://www.env-health.org/news/latest-news/article/bpa-classified-as-toxic, (accessed June 29, 2017, 2017).
46 EU finally recognises Bisphenol A as an endocrine disruptor for human health, http://www.env-health.org/resources/press-releases/article/eu-finally-recognises-bisphenol-a, (accessed June 16, 2017).
47 Technavio, *Global bis phenol-A market 2016–2020*, 2016.
48 Y. Q. Huang, C. K. C. Wong, J. S. Zheng, H. Bouwman, R. Barra, B. Wahlström, L. Neretin and M. H. Wong, *Environ. Int.*, 2012, **42**, 91–99.
49 J. Oehlmann, M. Oetken and U. Schulte-Oehlmann, *Environ. Res.*, 2008, **108**, 140–149.

50 J. A. Brotons, M. F. Olea-Serrano, M. Villalobos, V. Pedraza and N. Olea, *Environ. Health Perspect.*, 1995, **103**, 608–612.
51 J. Rajasärkkä, M. Pernica, J. Kuta, J. Lašňák, Z. Šimek and L. Bláha, *Water Res.*, 2016, **103**, 133–140.
52 Plastics Europe: Association of Plastics Manufacturers, Applications of Bisphenol A, http://www.bisphenol-a-europe.org/uploads/BPA applications.pdf.
53 B. Bae, J. H. Jeong and S. J. Lee, *Water Sci. Technol.*, 2002, **46**, 381–387.
54 T. Urase and K. Miyashita, *J. Mater. Cycles Waste Manage.*, 2003, **5**, 0077–0082.
55 O. Takahashi and S. Oishi, *Environ. Health Perspect.*, 2000, **108**, 931–935.
56 I. F. S. A. N. (INFOSAN), Bisphenol A (BPA) - Current state of knowledge and future actions by WHO and FAO, Report INFOSAN Information Note No. 5/2009 - Bisphenol A, World Health Organization, 2009.
57 D.-C. Wang, C.-Y. Wang, W.-Y. Chiu and L.-W. Chen, *J. Polym. Res.*, 1997, **4**, 9–16.
58 *Chemical Economics Handbook: Bisphenol A*, IHS Markit, 2016.
59 R. P. Pohanish, *Sittig's Handbook of Toxic and Hazardous Chemicals and Carcinogens*, Elsevier Inc., Oxford, UK, Sixth edn., 2012.
60 T. Yamamoto and A. Yasuhara, *Chemosphere*, 1999, **38**, 2569–2576.
61 H. Asakura, T. Matsuto and N. Tanaka, *Waste Manage.*, 2004, **24**, 613–622.
62 Y. Takao, H. C. Lee, S. Kohra and K. Arizono, *J. Health Sci.*, 2002, **48**, 331–334.
63 A. Goodson, W. Summerfield and I. Cooper, *Food Addit. Contam.*, 2002, **19**, 796–802.
64 M. A. Kamrin, *Medscape Gen. Med.*, 2004, **6**, 7.
65 F. S. vom Saal, S. Parmigiani, P. L. Palanza, L. G. Everett and R. Ragaini, *Environ. Res.*, 2008, **108**, 127–130.
66 M.-K. Yeo and M. Kang, *Water Res.*, 2006, **40**, 1906–1914.
67 J. Carlisle, D. Chan, M. Golub, S. Henkel, P. Painter and K. L. Wu, *Toxicological Profile for Bisphenol A*, Integrated Risk Assessment Branch Office of Environmental Health Hazard Assessment California Environmental Protection Agency, Sacramento, 2009, http://www.opc.ca.gov/webmaster/ftp/project_pages/MarineDebris_OEHHA_ToxProfiles/Bisphenol%20A%20Final.pdf.
68 L. N. Vandenberg, R. Hauser, M. Marcus, N. Olea and W. V. Welshons, *Reprod. Toxicol.*, 2007, **24**, 139–177.
69 C. Nerín, C. Fernández, C. Domeño and J. Salafranca, *J. Agric. Food Chem.*, 2003, **51**, 5647–5653.
70 T. Yamamoto and A. Yasuhara, *Bunseki Kagaku*, 2000, **49**, 443–447.
71 J. Sajiki and J. Yonekubo, *Chemosphere*, 2003, **51**, 55–62.
72 T. T. Schug, A. F. Johnson, L. S. Birnbaum, T. Colborn, L. J. G. Jr., D. P. Crews, T. Collins, A. M. Soto, F. S. v. Saal, J. A. McLachlan, C. Sonnenschein and J. J. Heindel, *Mol. Endocrinol.*, 2016, **30**, 833–847.
73 E. Diamanti-Kandarakis, J.-P. Bourguignon, L. C. Giudice, R. Hauser, G. S. Prins, A. M. Soto, R. T. Zoeller and A. C. Gore, *Endocr. Rev.*, 2009, **30**, 293–342.
74 D. A. Crain, M. Eriksen, T. Iguchi, S. Jobling, H. Laufer, G. A. LeBlanc and L. J. Guillette, *Reprod. Toxicol.*, 2007, **24**, 225–239.
75 H. Cabana, J. P. Jones and S. N. Agathos, *Eng. Life Sci.*, 2007, **7**, 429–456.
76 J. Corrales, L. A. Kristofco, W. B. Steele, B. S. Yates, C. S. Breed, E. S. Williams and B. W. Brooks, *Dose-Response*, 2015, **13**, 1–29.
77 E. A. Miska and A. C. Ferguson-Smith, *Science*, 2016, **354**, 59–63.
78 F. S. vom Saal and W. V. Welshons, *Mol. Cell. Endocrinol.*, 2014, **398**, 101–113.
79 N. Vandenberg Laura, A. Hunt Patricia, P. Myers John and S. vom Saal Frederick, *Rev. Environ. Health*, 2013, **28**, 37.
80 S. Eramo, G. Urbani, G. L. Sfasciotti, O. Brugnoletti, M. Bossù and A. Polimeni, *Ann. Stomatol.*, 2010, **1**, 14–21.
81 L. N. Vandenberg, I. Chahoud, J. J. Heindel, V. Padmanabhan, F. J. R. Paumgartten and G. Schoenfelder, *Environ. Health Perspect.*, 2010, **118**, 1055–1070.
82 T. Geens, D. Aerts, C. Berthot, J.-P. Bourguignon, L. Goeyens, P. Lecomte, G. Maghuin-Rogister, A.-M. Pironnet, L. Pussemier, M.-L. Scippo, J. Van Loco and A. Covaci, *Food Chem. Toxicol.*, 2012, **50**, 3725–3740.
83 N. Ben-Jonathan, E. R. Hugo and T. D. Brandebourg, *Mol. Cell. Endocrinol.*, 2009, **304**, 49–54.
84 S. S. Chang, *Rev. Urol.*, 2007, **9**, S13–S18.
85 K. Ćwiek-Ludwicka, *Rocz. Pantsw. Zakl. Hig.*, 2015, **66**, 299–307.
86 J. P. Myers, F. S. vom Saal, B. T. Akingbemi, K. Arizono, S. Belcher, T. Colborn, I. Chahoud, D. A. Crain, F. Farabollini, L. J. Guillette Jr., T. Hassold, S.-m. Ho, P. A. Hunt, T. Iguchi, S. Jobling, J. Kanno, H. Laufer, M. Marcus, J. A. McLachlan, A. Nadal, J. Oehlmann, N. Olea, P. Palanza, S. Parmigiani, B. S. Rubin, G. Schoenfelder, C. Sonnenschein, A. M. Soto, C. E. Talsness, J. A. Taylor, L. N. Vandenberg, J. G. Vandenbergh, S. Vogel, C. S. Watson, W. V. Welshons and R. T. Zoeller, *Environ. Health Perspect.*, 2009, **117**, 309–315.
87 Y. Luo, W. Guo, H. H. Ngo, L. D. Nghiem, F. I. Hai, J. Zhang, S. Liang and X. C. Wang, *Sci. Total Environ.*, 2014, 473–474, 619-641.
88 B. L. Loeb, C. M. Thompson, J. Drago, H. Takahara and S. Baig, *Ozone: Sci. Eng.*, 2012, **34**, 64–77.
89 S. Renou, J. G. Givaudan, S. Poulain, F. Dirassouyan and P. Moulin, *J. Hazard. Mater.*, 2008, **150**, 468–493.
90 Y. Peng, *Arabian J. Chem.*, 2017, **10**, S2567–S2574.
91 C. A. Staples, P. B. Dorn, G. M. Klecka, S. T. O'Block and L. R. Harris, *Chemosphere*, 1998, **36**, 2149–2173.
92 C. A. Richter, L. S. Birnbaum, F. Farabollini, R. R. Newbold, B. S. Rubin, C. E. Talsness,

J. G. Vandenbergh, D. R. Walser-Kuntz and F. S. vom Saal, *Reprod. Toxicol.*, 2007, **24**, 199–224.
93 H. Inadera, *Int. J. Med. Sci.*, 2015, **12**, 926–936.
94 U. V. Solmssen, *Chem. Rev.*, 1945, **37**, 481–598.
95 S. M. Rhind, *Philos. Trans. R. Soc., B*, 2009, **364**, 3391–3401.
96 T. M. Edwards and J. P. Myers, *Environ. Health Perspect.*, 2007, **115**, 1264–1270.
97 E. Swedenborg, J. Rüegg, S. Mäkelä and I. Pongratz, *J. Mol. Endocrinol.*, 2009, **43**, 1–10.
98 B. O. Clarke and S. R. Smith, *Environ. Int.*, 2011, **37**, 226–247.
99 A. Kelessidis and A. S. Stasinakis, *Waste Manage.*, 2012, **32**, 1186–1195.
100 D. Fytili and A. Zabaniotou, *Renewable Sustainable Energy Rev.*, 2008, **12**, 116–140.
101 S. Kanuga, *J. Am. Dent. Assoc.*, 2014, **145**, 1272–1273.
102 G. Gaustad, E. Olivetti and R. Kirchain, *Resour., Conserv. Recycl.*, 2012, **58**, 79–87.
103 *Aluminum Recycling and Processing for Energy Conservation and Sustainability*, ed. J. A. S. Green, ASM International, Materials Park, Ohio, 2007.
104 K. Tuppurainen, I. Halonen, P. Ruokojärvi, J. Tarhanen and J. Ruuskanen, *Chemosphere*, 1998, **36**, 1493–1511.
105 R. A. Keri, S.-M. Ho, P. A. Hunt, K. E. Knudsen, A. M. Soto and G. S. Prins, *Reprod. Toxicol.*, 2007, **24**, 240–252.
106 D. D. Seachrist, K. W. Bonk, S.-M. Ho, G. S. Prins, A. M. Soto and R. A. Keri, *Reprod. Toxicol.*, 2016, **59**, 167–182.
107 J.-H. Kang, Y. Katayama and F. Kondo, *Toxicology*, 2006, **217**, 81–90.
108 J.-H. Kang, F. Kondo and Y. Katayama, *Toxicology*, 2006, **226**, 79–89.
109 J.-H. Kang, D. Aasi and Y. Katayama, *Crit. Rev. Toxicol.*, 2007, **37**, 607–625.
110 M. Staniszewska, L. Falkowska, P. Grabowski, J. Kwaśniak, S. Mudrak-Cegiołka, A. R. Reindl, A. Sokołowski, E. Szumiło and A. Zgrundo, *Arch. Environ. Contam. Toxicol.*, 2014, **67**, 335–347.
111 C. Basheer, H. K. Lee and K. S. Tan, *Mar. Pollut. Bull.*, 2004, **48**, 1145–1167.
112 A. Belfroid, M. van Velzen, B. van der Horst and D. Vethaak, *Chemosphere*, 2002, **49**.
113 *The New Plastics Economy: Rethinking the Future of Plastics*, World Economic Forum, Ellen MacArthur Foundation and McKinsey & Company, 2016, http://www.ellenmacarthurfoundation.org/publications.
114 J. Sajiki and J. Yonekubo, *Chemosphere*, 2004, **55**, 861–867.
115 J.-H. Kang and F. Kondo, *Chemosphere*, 2005, **60**, 1288–1292.
116 A. B. Hansen and P. Lassen, *Screening of phenolic substances in the Nordic environments*, Nordic Council of Ministers, Tema Nord, 2008.
117 G. Funakoshi and S. Kasuya, *Chemosphere*, 2009, **75**, 491–497.
118 M. Ike, M. Y. Chen, E. Danzl, K. Sei and M. Fujita, *Water Sci. Technol.*, 2006, **53**, 153–159.
119 S. Schenker, M. Scheringer and K. Hungerbühler, *Environ. Sci. Technol.*, 2014, **48**, 5017–5024.
120 F. S. vom Saal, B. T. Akingbemi, S. M. Belcher, L. S. Birnbaum, D. A. Crain, M. Eriksen, F. Farabollini, L. J. Guillette, R. Hauser, J. J. Heindel, S.-M. Ho, P. A. Hunt, T. Iguchi, S. Jobling, J. Kanno, R. A. Keri, K. E. Knudsen, H. Laufer, G. A. LeBlanc, M. Marcus, J. A. McLachlan, J. P. Myers, A. Nadal, R. R. Newbold, N. Olea, G. S. Prins, C. A. Richter, B. S. Rubin, C. Sonnenschein, A. M. Soto, C. E. Talsness, J. G. Vandenbergh, L. N. Vandenberg, D. R. Walser-Kuntz, C. S. Watson, W. V. Welshons, Y. Wetherill and R. T. Zoeller, *Reprod. Toxicol.*, 2007, **24**, 131–138.
121 *NHANES 2003–2004 Laboratory Data: Environmental Phenols*, Centers for Disease Control and Prevention, 2003–2004, https://wwwn.cdc.gov/Nchs/Nhanes/2003-2004/L24EPH_C.htm.
122 R. Kuruto-Niwa, Y. Tateoka, Y. Usuki and R. Nozawa, *Chemosphere*, 2007, **66**, 1160–1164.
123 X. Ye, Z. Kuklenyik, L. L. Needham and A. M. Calafat, *J. Chromatogr. B: Anal. Technol. Biomed. Life Sci.*, 2006, **831**, 110–115.
124 Y. Tateoka, *J. Hum. Lact.*, 2014, **31**, 474–478.
125 D. W. Kolpin, E. T. Furlong, M. T. Meyer, E. M. Thurman, S. D. Zaugg, L. B. Barber and H. T. Buxton, *Environ. Sci. Technol.*, 2002, **36**, 1202–1211.
126 C. C. Montagner and W. F. Jardim, *J. Braz. Chem. Soc.*, 2011, **22**, 1452–1462.
127 C. Tang, J. Chen and Y. Zhang, *Fresenius Environ. Bull.*, 2012, **21**, 3911–3919.
128 D. d. A. Azevedo, S. Lacorte, P. Viana and D. Barceló, *J. Braz. Chem. Soc.*, 2001, **12**, 532–537.
129 A. Colin, C. Bach, C. Rosin, J.-F. Munoz and X. Dauchy, *Arch. Environ. Contam. Toxicol.*, 2014, **66**, 86–99.
130 H. M. Kuch and K. Ballschmiter, *Environ. Sci. Technol.*, 2001, **35**.
131 V. A. Santhi, N. Sakai, E. D. Ahmad and A. M. Mustafa, *Sci. Total Environ.*, 2012, **427**, 332–338.
132 N. Casajuana and S. Lacorte, *Chromatographia*, 2003, **57**, 649–655.
133 T. T. Makinwa and P. O. Uadia, *World Environ.*, 2015, **5**, 135–139.
134 J.-Y. Hu, T. Aizawa and S. Ookubo, *Environ. Sci. Technol.*, 2002, **36**, 1980–1987.
135 T. Yamamoto and A. Yasuhara, *Chemosphere*, 2002, **46**, 1215–1223.
136 J.-H. Kang, K. Kito and F. Kondo, *J. Food Prot.*, 2003, **66**, 1444–1447.
137 A. Davis and J. H. Golden, *J. Chromatogr., A*, 1967, **26**, 254–255.
138 S. R. Howe and L. Borodinsky, *Food Addit. Contam.*, 1998, **15**, 370–375.
139 E. M. Munguia-Lopez and H. Soto-Valdez, *J. Agric. Food Chem.*, 2001, **49**, 3666–3671.

140 C. Liao and K. Kannan, *Environ. Sci. Technol.*, 2011, **45**, 9372–9379.
141 J. López-Cervantes and P. Paseiro-Losada, *Food Addit. Contam.*, 2003, **20**, 596–606.
142 N. Olea, R. Pulgar, P. Pérez, F. Olea-Serrano, A. Rivas, A. Novillo-Fertrell, V. Pedraza, A. M. Soto and C. Sonnenschein, *Environ. Health Perspect.*, 1996, **104**, 298–305.
143 D. Arenholt-Bindslev, V. Breinholt, A. Preiss and G. Schmalz, *Clin. Oral Investig.*, 1999, **3**, 120–125.
144 J. B. Lewis, F. A. Rueggeberg, C. A. Lapp, J. W. Ergle and G. S. Schuster, *Clin. Oral Investig.*, 1999, **3**, 107–113.
145 M. Noda, H. Komatsu and H. Sano, *J. Biomed. Mater. Res.*, 1999, **47**, 374–378.
146 G. Schmalz, A. Preiss and D. Arenholt-Bindslev, *Clin. Oral Investig.*, 1999, **3**, 114–119.
147 E. Y. K. Fung, N. O. Ewoldsen, H. A. J. St. Germain, D. B. Marx, C.-L. Miaw, C. Siew, H.-N. Chou, S. E. Gruninger and D. M. Meyer, *J. Am. Dent. Assoc.*, 2000, **131**, 51–58.
148 A. Zafra, M. del Olmo, R. Pulgar, A. Navalón and J. L. Vílchez, *Chromatographia*, 2002, **56**, 213–218.
149 A. S. Al-Hiyasat, H. Darmani and A. M. Elbetieha, *Eur. J. Oral Sci.*, 2004, **112**, 267–272.
150 N. Sasaki, K. Okuda, T. Kato, H. Kakishima, H. Okuma, K. Abe, H. Tachino, K. Tuchida and K. Kubono, *J. Mater. Sci.: Mater. Med.*, 2005, **16**, 297–300.
151 R. Joskow, D. B. Barr, J. R. Barr, A. M. Calafat, L. L. Needham and C. Rubin, *J. Am. Dent. Assoc.*, 2006, **137**, 353–362.
152 J. L. Carwile, H. T. Luu, L. S. Bassett, D. A. Driscoll, C. Yuan, J. Y. Chang, X. Ye, A. M. Calafat and K. B. Michels, *Environ. Health Perspect.*, 2009, **117**, 1368–1372.
153 E. M. Munguia-Lopez, E. Peralta, A. Gonzalez-Leon, C. Vargas-Requena and H. Soto-Valdez, *J. Agric. Food Chem.*, 2002, **50**, 7299–7302.
154 R. Braunrath, D. Podlipna, S. Padlesak and M. Cichna-Markl, *J. Agric. Food Chem.*, 2005, **53**, 8911–8917.
155 L. Grumetto, D. Montesano, S. Seccia, S. Albrizio and F. Barbato, *J. Agric. Food Chem.*, 2008, **56**, 10633–10637.
156 J. Yonekubo, K. Hayakawa and J. Sajiki, *J. Agric. Food Chem.*, 2008, **56**, 2041–2047.
157 J. E. Biles, T. P. McNeal, T. H. Begley and H. C. Hollifield, *J. Agric. Food Chem.*, 1997, **45**, 3541–3544.
158 G. D. Bittner, C. Z. Yang and M. A. Stoner, *Environ. Health*, 2014, **13**, 41–41.
159 Y. Sun, M. Wada, O. Al-Dirbashi, N. Kuroda, H. Nakazawa and K. Nakashima, *J. Chromatogr. B: Biomed. Sci. Appl.*, 2000, **749**, 49–56.
160 A. D'Antuono, V. C. Dall'Orto, A. L. Balbo, S. Sobral and I. Rezzano, *J. Agric. Food Chem.*, 2001, **49**, 1098–1101.
161 C. Brede, P. Fjeldal, I. Skjevrak and H. Herikstad, *Food Addit. Contam.*, 2003, **20**, 684–689.
162 Y. Takao, H. C. Lee, Y. Ishibashi, S. Kohra, N. Tominaga and K. Arizono, *J. Health Sci.*, 1999, **45**, P39–P39.
163 C. Cox, *Kicking the Can? Major Retailers Still Selling Canned Food with Toxic BPA*, Center for Environmental Health, Oakland, CA, 2017.
164 J.-H. Kang and F. Kondo, *Food Addit. Contam.*, 2002, **19**, 886–890.
165 X.-L. Cao, J. Corriveau and S. Popovic, *J. Agric. Food Chem.*, 2009, **57**, 1307–1311.
166 A. K. Sakhi, I. T. L. Lillegaard, S. Voorspoels, M. H. Carlsen, E. B. Løken, A. L. Brantsæter, M. Haugen, H. M. Meltzer and C. Thomsen, *Environ. Int.*, 2014, **73**, 259–269.
167 J. E. Biles, T. P. McNeal and T. H. Begley, *J. Agric. Food Chem.*, 1997, **45**, 4697–4700.
168 L. K. Ackerman, G. O. Noonan, W. M. Heiserman, J. A. Roach, W. Limm and T. H. Begley, *J. Agric. Food Chem.*, 2010, **58**, 2307–2313.
169 X.-L. Cao, G. Dufresne, S. Belisle, G. Clement, M. Falicki, F. Beraldin and A. Rulibikiye, *J. Agric. Food Chem.*, 2008, **56**, 7919–7924.
170 H.-W. Kuo and W.-H. Ding, *J. Chromatogr., A*, 2004, **1027**, 67–74.
171 B. M. Thomson and P. R. Grounds, *Food Addit. Contam.*, 2005, **22**, 65–72.
172 N. Rastkari, M. Yunesian and R. Ahmadkhaniha, *Iran. J. Environ. Health. Sci. Eng.*, 2011, **8**, 95–100.
173 N. C. Maragou, E. N. Lampi, N. S. Thomaidis and M. A. Koupparis, *J. Chromatogr., A*, 2006, **1129**, 165–173.
174 T. Yoshida, M. Horie, Y. Hoshino, H. Nakazawa, M. Horie and H. Nakazawa, *Food Addit. Contam.*, 2001, **18**, 69–75.
175 B. S. Shin, C. H. Kim, Y. S. Jun, D. H. Kim, B. M. Lee, C. H. Yoon, E. H. Park, K. C. Lee, S.-Y. Han, K. L. Park, H. S. Kim and S. D. Yoo, *J. Toxicol. Environ. Health, Part A*, 2004, **67**, 1971–1985.
176 D. Zalko, C. Jacques, H. Duplan, S. Bruel and E. Perdu, *Chemosphere*, 2011, **82**, 424–430.
177 S. Biedermann, P. Tschudin and K. Grob, *Anal. Bioanal. Chem.*, 2010, **398**, 571–576.
178 S.-Y. Lu, W.-J. Chang, S. O. Sojinu and H.-G. Ni, *Chemosphere*, 2013, **92**, 1190–1194.
179 A. M. Hormann, F. S. vom Saal, S. C. Nagel, R. W. Stahlhut, C. L. Moyer, M. R. Ellersieck, W. V. Welshons, P.-L. Toutain and J. A. Taylor, *PLoS One*, 2014, **9**, e110509.
180 T. Mendum, E. Stoler, H. VanBenschoten and J. C. Warner, *Green Chem. Lett. Rev.*, 2011, **4**, 81–86.
181 T. Geens, L. Goeyens, K. Kannan, H. Neels and A. Covaci, *Sci. Total Environ.*, 2012, **435–436**, 30–33.
182 M. R. Bernier and L. N. Vandenberg, *PLoS One*, 2017, **12**, e0178449.
183 N. K. Wilson, J. C. Chuang, C. Lyu, R. Menton and M. K. Morgan, *J. Exposure Anal. Environ. Epidemiol.*, 2003, **13**, 187–202.
184 N. K. Wilson, J. C. Chuang, M. K. Morgan, R. A. Lordo and L. S. Sheldon, *Environ. Res.*, 2007, **103**, 9–20.
185 N. K. Wilson, J. C. Chuang and C. Lyu, *J. Exposure Anal. Environ. Epidemiol.*, 2001, **11**, 449–458.

186 P. Fu and K. Kawamura, *Environ. Pollut.*, 2010, **158**, 3138–3143.
187 C. Liao, F. Liu, Y. Guo, H.-B. Moon, H. Nakata, Q. Wu and K. Kannan, *Environ. Sci. Technol.*, 2012, **46**, 9138–9145.
188 R. A. Rudel, J. G. Brody, J. D. Spengler, J. Vallarino, P. W. Geno, G. Sun and A. Yau, *J. Air Waste Manage. Assoc.*, 2001, **51**, 499–513.
189 R. A. Rudel, D. E. Camann, J. D. Spengler, L. R. Korn and J. G. Brody, *Environ. Sci. Technol.*, 2003, **37**, 4543–4553.
190 T. Oka and Y. Oshige, *Anal. Sci.*, 2000, **16**, 1071–1076.
191 A. Vivacqua, A. G. Recchia, G. Fasanella, S. Gabriele, A. Carpino, V. Rago, M. L. Di Gioia, A. Leggio, D. Bonofiglio, A. Liguori and M. Maggiolini, *Endocrine*, 2003, **22**, 275–284.
192 K. Inoue, S. Murayama, K. Takeba, Y. Yoshimura and H. Nakazawa, *J. Food Compos. Anal.*, 2003, **16**, 497–506.
193 X.-L. Cao, J. Corriveau, S. Popovic, G. Clement, F. Beraldin and G. Dufresne, *J. Agric. Food Chem.*, 2009, **57**, 5345–5351.
194 A. G. Asimakopoulos, M. Elangovan and K. Kannan, *Environ. Sci. Technol.*, 2016, **50**, 13539–13547.
195 J. Sajiki, R. Yanagibori and Y. Kobayashi, *Nippon Eiseigaku Zasshi*, 2010, **65**, 467–470.
196 P. Viñas, I. López-García, N. Campillo, R. E. Rivas and M. Hernández-Córdoba, *Anal. Bioanal. Chem.*, 2012, **404**, 671–678.
197 E. S. Kwak, A. Just, R. Whyatt and R. L. Miller, *Open Allergy J.*, 2009, **2**, 45–50.
198 R. E. Dodson, M. Nishioka, L. J. Standley, L. J. Perovich, J. G. Brody and R. A. Rudel, *Environ. Health Perspect.*, 2012, **120**, 935–943.
199 A. Myridakis, E. Fthenou, E. Balaska, M. Vakinti, M. Kogevinas and E. G. Stephanou, *Environ. Int.*, 2015, **83**, 1–10.
200 C. Liao and K. Kannan, *Environ. Sci. Technol.*, 2011, **45**, 6761–6768.
201 W. J. Jackson, Jr. and W. R. Darnell, *US Pat.*, 4507256, 1983.
202 M. Gehring, L. Tennhardt, d. Vogel, D. Weltin and B. Bilitewski, in *Waste Management and the Environment II. WIT Transactions on Ecology and the Environment*, ed. C. A. Brebbia, S. Kungulos, V. Popov and H. Itoh, WIT Press, Southampton, Boston, 2004, vol. 78, ch. 294, pp. 294–300.
203 H. Fukazawa, K. Hoshino, T. Shiozawa, H. Matsushita and Y. Terao, *Chemosphere*, 2001, **44**, 973–979.
204 A. Ozaki, Y. Yamaguchi, T. Fujita, K. Kuroda and G. Endo, *Food Chem. Toxicol.*, 2004, **42**, 1323–1337.
205 A. M. Vinggaard, W. Körner, K. H. Lund, U. Bolz and J. H. Petersen, *Chem. Res. Toxicol.*, 2000, **13**, 1214–1222.
206 M. J. Lopez-Espinosa, A. Granada, P. Araque, J. M. Molina-Molina, M. C. Puertollano, A. Rivas, M. Fernández, I. Cerrillo, M. F. Olea-Serrano, C. López and N. Olea, *Food Addit. Contam.*, 2007, **24**, 95–102.
207 K. Peltonen and J. Pukkila, *J. Chromatogr., A*, 1988, **439**, 375–380.
208 K. Peltonen, *J. Anal. Appl. Pyrolysis*, 1986, **10**, 51–57.
209 T. Zhang, J. Xue, C.-z. Gao, R.-l. Qiu, Y.-x. Li, X. Li, M.-z. Huang and K. Kannan, *Environ. Sci. Technol.*, 2016, **50**, 4045–4053.
210 X. Bi, B. R. T. Simoneit, Z. Wang, X. Wang, G. Sheng and J. Fu, *Atmos. Environ.*, 2010, **44**, 4440–4445.
211 T. Yamamoto, A. Yasuhara, H. Shiraishi and O. Nakasugi, *Chemosphere*, 2001, **42**, 415–418.
212 H. Yin, Y. Zhou, J. Xu, S. Ai, L. Cui and L. Zhu, *Anal. Chim. Acta*, 2010, **659**, 144–150.
213 H. Yin, L. Cui, S. Ai, H. Fan and L. Zhu, *Electrochim. Acta*, 2010, **55**, 603–610.
214 *Tox Town: Polyvinyl Chloride (PVC)*, U.S. National Library of Medicine Division of Specialized Information Services, Bethesda, 2017, https://toxtown.nlm.nih.gov/text_version/chemicals.php?id=84.
215 H. P. H. Arp, N. A. O. Morin, S. E. Hale, G. Okkenhaug, K. Breivik and M. Sparrevik, *Waste Manage.*, 2017, **60**, 775–785.
216 S. Lee, C. Liao, G.-J. Song, K. Ra, K. Kannan and H.-B. Moon, *Chemosphere*, 2015, **119**, 1000–1006.
217 *Screening Assessment for the Challenge: Phenol, 4,4'-(1-methylethylidene)bis-(Bisphenol A)*, Environment Canada and Health Canada, Ottowa, 2008, http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=3C756383-1.
218 *Consultation Document: Phenol, 4,4'-(1-methylethylidene)bis-(Bisphenol A)*, Environment Canada, Gatineau, Quebec, 2009, https://www.ec.gc.ca/lcpe-cepa/79A93C66-1EE0-4F72-89C1-114DFD7B7292/pba-eng.pdf.
219 M. Wright-Walters, C. Volz, E. Talbott and D. Davis, *Sci. Total Environ.*, 2011, **409**, 676–685.
220 USEPA, *Advancing sustainable Materials Management: Facts and Figures*, United States Environmental Protection Agency Office of Land and Emergency Management, 2014, https://www.epa.gov/sites/production/files/2016-11/documents/2014_smmfactsheet_508.pdf.
221 B. Bilitewski, G. Härdtle and K. Marek, *Waste Management*, Springer, New York, 1997.
222 D. Vogel, B. Bilitewski and L. D. Nghiem, *Int. J. Environ. Waste Manage.*, 2007, **1**, 338–350.
223 J. Schwarzbauer, S. Heim, S. Brinker and R. Littke, *Water Res.*, 2002, **36**, 2275–2287.
224 T. Wintgens, M. Gallenkemper and T. Melin, *Water Sci. Technol.*, 2003, **48**, 127–134.
225 K. Yamada, T. Urase, T. Matsuo and N. Suzuki, *Mizu Kankyo Gakkaishi*, 1999, **22**, 40–45.
226 N. Morin, H. P. H. Arp and S. E. Hale, *Environ. Sci. Technol.*, 2015, **49**, 7675–7683.
227 N. Paxéus, *Water Sci. Technol.*, 2000, **42**, 323–333.
228 A. Rigol, A. Latorre, S. Lacorte and D. Barceló, *Environ. Toxicol. Chem.*, 2004, **23**, 339–347.
229 M. Fürhacker, S. Scharf and H. Weber, *Chemosphere*, 2000, **41**, 751–756.
230 H. Fukazawa, M. Watanabe, F. Shiraishi, H. Shiraishi, T. Shiozawa, H. Matsushita and Y. Terao, *J. Health Sci.*, 2002, **48**, 242–249.

231 J. Jackson and R. Sutton, *Sci. Total Environ.*, 2008, **405**, 153–160.
232 *Bisphenol A Alternatives in Thermal Paper*, U.S. Environmental Protection Agency, 2015, https://www.epa.gov/sites/production/files/2015-09/documents/bpa_ch5.pdf.
233 H.-B. Lee, T. E. Peart, J. Chan and G. Gris, *Water Qual. Res. J. Can.*, 2004, **39**, 57–63.
234 C. Höhne and W. Püttmann, *Environ. Sci. Pollut. Res.*, 2008, **15**, 405–416.
235 V. G. Samaras, A. S. Stasinakis, D. Mamais, N. S. Thomaidis and T. D. Lekkas, *J. Hazard. Mater.*, 2013, **244–245**, 259–267.
236 H. Zhou, X. Huang, X. Wang, X. Zhi, C. Yang, X. Wen, Q. Wang, H. Tsuno and H. Tanaka, *Environ. Monit. Assess.*, 2010, **161**, 107–121.
237 J. Zhao, Y. Li, C. Zhang, Q. Zeng and Q. Zhou, *J. Hazard. Mater.*, 2008, **155**, 305–311.
238 Z. Zhang, M. Le Velly, S. M. Rhind, C. E. Kyle, R. L. Hough, E. I. Duff and C. McKenzie, *Sci. Total Environ.*, 2015, **515–516**, 1–11.
239 K. A. Langdon, M. S. J. Warne, R. J. Smernik, A. Shareef and R. S. Kookana, *Sci. Total Environ.*, 2011, **409**, 1075–1081.
240 T. A. Ternes, H. Andersen, D. Gilberg and M. Bonerz, *Anal. Chem.*, 2002, **74**, 3498–3504.
241 O. Braga, G. A. Smythe, A. I. Schäfer and A. J. Feitz, *Environ. Sci. Technol.*, 2005, **39**, 3351–3358.
242 S. Chu and C. D. Metcalfe, *J. Chromatogr., A*, 2007, **1164**, 212–218.
243 S. Song, M. Song, L. Zeng, T. Wang, R. Liu, T. Ruan and G. Jiang, *Environ. Pollut.*, 2014, **186**, 14–19.
244 K. A. Hicks, M. L. M. Fuzzen, E. K. McCann, M. J. Arlos, L. M. Bragg, S. Kleywegt, G. R. Tetreault, M. E. McMaster and M. R. Servos, *Environ. Sci. Technol.*, 2017, **51**, 1811–1819.
245 H. Fromme, T. Küchler, T. Otto, K. Pilz, J. Müller and A. Wenzel, *Water Res.*, 2002, **36**, 1429–1438.
246 C. A. Kinney, E. T. Furlong, D. W. Kolpin, M. R. Burkhardt, S. D. Zaugg, S. L. Werner, J. P. Bossio and M. J. Benotti, *Environ. Sci. Technol.*, 2008, **42**, 1863–1870.
247 E. Z. Harrison, S. R. Oakes, M. Hysell and A. Hay, *Sci. Total Environ.*, 2006, **367**, 481–497.
248 D. P. Mohapatra, S. K. Brar, R. D. Tyagi and R. Y. Surampalli, *J. Xenobiot.*, 2011, **1**, 3.
249 J. Hall, in *Workshop on Problems Around Sludge: Proceedings*, ed. H. Langenkamp and L. Mamo, European Commission Joint Research Centre, 1999, ch. Session 3: Technology and innovative options related to sludge management, pp. 155–172.
250 NeBRA, *A National Biosolids Regulation, Quality, End Use and Disposal Survey (Final Report)*, North East Biosolids and Residuals Association (NEBRA), Tamworth, NH, 2007.
251 S. M. Rhind, C. E. Kyle, H. Ruffie, E. Calmettes, M. Osprey, Z. L. Zhang, D. Hamilton and C. McKenzie, *Environ. Pollut.*, 2013, **181**, 262–270.
252 R. E. Alcock, S. P. McGrath and K. C. Jones, *Environ. Toxicol. Chem.*, 1995, **14**, 553–560.
253 E. Eljarrat, G. Marsh, A. Labandeira and D. Barceló, *Chemosphere*, 2008, **71**, 1079–1086.
254 M.-J. Wang, S. P. McGrath and K. C. Jones, *Environ. Sci. Technol.*, 1995, **29**, 356–362.
255 K. A. Langdon, M. S. J. Warne, R. J. Smernik, A. Shareef and R. S. Kookana, *Chemosphere*, 2012, **86**, 1050–1058.
256 K. A. Langdon, M. S. Warne, R. J. Smernik, A. Shareef and R. S. Kookana, *Sci. Total Environ.*, 2013, **447**, 56–63.
257 C. Paul, S. M. Rhind, C. E. Kyle, H. Scott, C. McKinnell and R. M. Sharpe, *Environ. Health Perspect.*, 2005, **113**, 1580–1587.
258 H. W. Erhard and S. M. Rhind, *Sci. Total Environ.*, 2004, **332**, 101–108.
259 P. A. Fowler, N. J. Dorà, H. McFerran, M. R. Amezaga, D. W. Miller, R. G. Lea, P. Cash, A. S. McNeilly, N. P. Evans, C. Cotinot, R. M. Sharpe and S. M. Rhind, *Mol. Hum. Reprod.*, 2008, **14**, 269–280.
260 P. M. Lind, M. Gustafsson, S. A. B. Hermsen, S. Larsson, C. E. Kyle, J. Örberg and S. M. Rhind, *Sci. Total Environ.*, 2009, **407**, 2200–2208.
261 M. Bellingham, P. A. Fowler, M. R. Amezaga, S. M. Rhind, C. Cotinot, B. Mandon-Pepin, R. M. Sharpe and N. P. Evans, *Environ. Health Perspect.*, 2009, **117**, 1556–1562.
262 M. Bellingham, P. A. Fowler, M. R. Amezaga, C. M. Whitelaw, S. M. Rhind, C. Cotinot, B. Mandon-Pepin, R. M. Sharpe and N. P. Evans, *J. Neuroendocrinol.*, 2010, **22**, 527–533.
263 P. M. Lind, D. Öberg, S. Larsson, C. E. Kyle, J. Örberg and S. M. Rhind, *Sci. Total Environ.*, 2010, **408**, 2340–2346.
264 M. Bellingham, M. R. Amezaga, B. Mandon-Pepin, C. J. B. Speers, C. E. Kyle, N. P. Evans, R. M. Sharpe, C. Cotinot, S. M. Rhind and P. A. Fowler, *Mol. Cell. Endocrinol.*, 2013, **376**, 156–172.
265 R. G. Lea, M. R. Amezaga, B. Loup, B. Mandon-Pépin, A. Stefansdottir, P. Filis, C. Kyle, Z. Zhang, C. Allen, L. Purdie, L. Jouneau, C. Cotinot, S. M. Rhind, K. D. Sinclair and P. A. Fowler, *Sci. Rep.*, 2016, **6**, 22279.
266 S. Hombach-Klonisch, A. Danescu, F. Begum, M. R. Amezaga, S. M. Rhind, R. M. Sharpe, N. P. Evans, M. Bellingham, C. Cotinot, B. Mandon-Pepin, P. A. Fowler and T. Klonisch, *Mol. Cell. Endocrinol.*, 2013, **367**, 98–108.
267 R. L. Hough, P. Booth, L. M. Avery, S. Rhind, C. Crews, J. Bacon, C. D. Campbell and D. Tompkins, *Waste Manage.*, 2012, **32**, 117–130.
268 L. K. Dodgen, J. Li, D. Parker and J. J. Gan, *Environ. Pollut.*, 2013, **182**, 150–156.
269 S. Sidhu, B. Gullett, R. Striebich, J. Klosterman, J. Contreras and M. DeVito, *Atmos. Environ.*, 2005, **39**, 801–811.
270 M. Šala, Y. Kitahara, S. Takahashi and T. Fujii, *Chemosphere*, 2010, **78**, 42–45.
271 Y. Kitahara, S. Takahashi, M. Tsukagoshi and T. Fujii, *Chemosphere*, 2010, **80**, 1281–1284.

272 L.-H. Lee, *J. Polym. Sci., Part A: Gen. Pap.*, 1964, **2**, 2859–2873.
273 S. Tsuge, T. Okumoto, Y. Sugimura and T. Takeuchi, *J. Chromatogr. Sci.*, 1969, **7**, 253–256.
274 Y. Ito, H. Ogasawara, Y. Ishida, H. Ohtani and S. Tsuge, *Polym. J.*, 1996, **28**, 1090–1095.
275 C. Puglisi, L. Sturiale and G. Montaudo, *Macromolecules*, 1999, **32**, 2194–2203.
276 M. Blazsó, *Polymer*, 1991, **32**, 590–596.
277 H. Nakagawa, S. Wakatsuka, S. Tsuge and T. Koyama, *Polym. J.*, 1988, **20**, 9–16.
278 N. Grassie, M. I. Guy and N. H. Tennent, *Polym. Degrad. Stab.*, 1986, **14**, 125–137.
279 H. Nakagawa, S. Tsuge and T. Koyama, *J. Anal. Appl. Pyrolysis*, 1987, **12**, 97–113.
280 R. E. Miller, *US Pat.*, 4147531, 1979.
281 N. R. C. U. C. o. H. E. o. W. Incineration, in *Waste Incineration & Public Health*, National Academies Press, Washington, DC, 2000, vol. 3.
282 T. A. Association, *Aluminum: The Element of Sustainability: A North American Aluminum Industry Sustainability Report*, 2011.
283 J. P. Aittola, J. Paasivirta and A. Vattulainen, *Chemosphere*, 1993, **27**, 65–72.
284 *European Union Risk Assessment Report, 4,4'-Isopropylidenediphenol (Bisphenol-A)*, European Commission-Joint Research Centre, Institute for Health and Consumer Protection, Luxembourg, 2008.
285 L. B. Barber, G. K. Brown and S. D. Zaugg, in *Analysis of Environmental Endocrine Disruptors*, American Chemical Society, 1999, vol. 747, ch. 7, pp. 97–123.
286 USEPA, *Wastewater Technology Fact Sheet: Chlorine Disinfection*, United States Environmental Protection Agency Office of Water, 1999, https://www3.epa.gov/npdes/pubs/chlo.pdf.
287 R. Bolger, T. E. Wiese, K. Ervin, S. Nestich and W. Checovich, *Environ. Health Perspect.*, 1998, **106**, 551–557.
288 R. Kuruto-Niwa, Y. Terao and R. Nozawa, *Environ. Toxicol. Pharmacol.*, 2002, **12**, 27–35.
289 Y. Yang, L. Lu, J. Zhang, Y. Yang, Y. Wu and B. Shao, *J. Chromatogr., A*, 2014, **1328**, 26–34.
290 S. Chu, G. D. Haffner and R. J. Letcher, *J. Chromatogr., A*, 2005, **1097**, 25–32.
291 G. Mascolo, V. Locaputo and G. Mininni, *J. Chromatogr., A*, 2010, **1217**, 4601–4611.
292 *Micropollutants in municipal wastewater: Processes for advanced removal in wastewater treatment plants*, The Swiss Federal Office for the Environment, Bern, 2012, https://www.bafu.admin.ch/bafu/en/home/topics/water/water--publications/publications-water/micropollutants-municipal-wastewater-summary.html.
293 J. Margot, C. Kienle, A. Magnet, M. Weil, L. Rossi, L. F. de Alencastro, C. Abegglen, D. Thonney, N. Chèvre, M. Schärer and D. A. Barry, *Sci. Total Environ.*, 2013, **461–462**, 480–498.
294 Y. Yoon, P. Westerhoff, S. A. Snyder and M. Esparza, *Water Res.*, 2003, **37**, 3530–3537.
295 I. Gültekin, V. Mavrov and N. H. Ince, *J. Adv. Oxid. Technol.*, 2009, **12**, 242–248.
296 S. Baig, G. Hansmann and B. Paolini, *Water Sci. Technol.*, 2008, **58**, 451–458.
297 M. Deborde, S. Rabouan, P. Mazellier, J.-P. Duguet and B. Legube, *Water Res.*, 2008, **42**, 4299–4308.
298 T. Kamiya, T. Yamauchi, J. Hirotsuji and M. Fujita, *Ozone: Sci. Eng.*, 2005, **27**, 389–395.
299 M. Deborde, S. Rabouan, J.-P. Duguet and B. Legube, *Environ. Sci. Technol.*, 2005, **39**, 6086–6092.
300 P.-O. Nordström and G. O'Kelly, *Tighter recycled fiber markets: Softwood strikes back!*, McKinsey&Company, 2013.
301 K. Pivnenko, D. Laner and T. F. Astrup, *Environ. Sci. Technol.*, 2016, **50**, 12302–12311.
302 J. Morris, *Int. J. Life Cycle Assess.*, 2005, **10**, 273–284.
303 K. R. Bruce, L. O. Beach and B. K. Gullett, *Waste Manage.*, 1991, **11**, 97–102.
304 B. K. Gullett, K. R. Bruce, L. O. Beach and A. M. Drago, *Chemosphere*, 1992, **25**, 1387–1392.
305 E. P. Management, *pH Measurement in Deinking Mills (Secondary Fiber)*, Pulp and Paper, 2013.
306 M. Suhr, G. Klein, I. Kourti, M. R. Gonzalo, G. G. Santonja, S. Roudier and L. D. Sancho, Best Available Technologies (BAT) Reference Document for the Production of Pu, *lp, Paper and Board*, European Commission Joint Research Centre Institute for Prospective Technological Studies, Luxembourg, 2015.
307 L. Truong, M. A. DeNardo, S. Kundu, T. J. Collins and R. L. Tanguay, *Green Chem.*, 2013, **15**, 2339–2343.
308 W. C. Ellis, C. T. Tran, R. Roy, M. Rusten, A. Fischer, A. D. Ryabov, B. Blumberg and T. J. Collins, *J. Am. Chem. Soc.*, 2010, **132**, 9774–9781.
309 S. S. Gupta, M. Stadler, C. A. Noser, A. Ghosh, B. Steinhoff, D. Lenoir, C. P. Horwitz, K.-W. Schramm and T. J. Collins, *Science*, 2002, **296**, 326–328.
310 C. Wang, J. Gao and C. Gu, *Environ. Sci. Technol.*, 2017, **51**, 488–496.
311 T. J. Collins, *Acc. Chem. Res.*, 2002, **35**, 782–790.
312 A. Chanda, D.-L. Popescu, F. T. de Oliveira, E. L. Bominaar, A. D. Ryabov, E. Münck and T. J. Collins, *J. Inorg. Biochem.*, 2006, **100**, 606–619.
313 D. Banerjee, F. M. Apollo, A. D. Ryabov and T. J. Collins, *Chem. – Eur. J.*, 2009, **15**, 10199–10209.
314 A. D. Ryabov and T. J. Collins, *Adv. Inorg. Chem.*, 2009, **61**, 471–521.
315 T. J. Collins, S. K. Khetan and A. D. Ryabov, in *Handbook of Green Chemistry*, ed. P. T. Anastas and R. H. Crabtree, WILEY-VCH Verlag GmbH & KgaA, Weinheim, 2009, ch. 3, pp. 39–77.
316 S. Kundu, A. Chanda, J. V. K. Thompson, G. Diabes, S. K. Khetan, A. D. Ryabov and T. J. Collins, *Catal. Sci. Technol.*, 2015, **5**, 1775–1782.

317 L. Q. Shen, E. S. Beach, Y. Xiang, D. J. Tshudy, N. Khanina, C. P. Horwitz, M. E. Bier and T. J. Collins, *Environ. Sci. Technol.*, 2011, **45**, 7882–7887.
318 A. Chanda, S. K. Khetan, D. Banerjee, A. Ghosh and T. J. Collins, *J. Am. Chem. Soc.*, 2006, **128**, 12058–12059.
319 S. Kundu, A. Chanda, L. Espinosa-Marvan, S. K. Khetan and T. J. Collins, *Catal. Sci. Technol.*, 2012, **2**, 1165–1172.
320 L. L. Tang, M. A. DeNardo, C. Gayathri, R. R. Gil, R. Kanda and T. J. Collins, *Environ. Sci. Technol.*, 2016, **50**, 5261–5268.
321 L. L. Tang, M. A. DeNardo, C. J. Schuler, M. R. Mills, C. Gayathri, R. R. Gil, R. Kanda and T. J. Collins, *J. Am. Chem. Soc.*, 2017, **139**, 879–887.
322 S. Kundu, A. Chanda, S. K. Khetan, A. D. Ryabov and T. J. Collins, *Environ. Sci. Technol.*, 2013, **47**, 5319–5326.
323 D. Banerjee, A. L. Markley, T. Yano, A. Ghosh, P. B. Berget, E. G. Minkley, S. K. Khetan and T. J. Collins, *Angew. Chem., Int. Ed.*, 2006, **45**, 3974–3977.
324 C. P. Horwitz, D. R. Fooksman, L. D. Vuocolo, S. W. Gordon-Wylie, N. J. Cox and T. J. Collins, *J. Am. Chem. Soc.*, 1998, **120**, 4867–4868.
325 N. Chahbane, D.-L. Popescu, D. A. Mitchell, A. Chanda, D. Lenoir, A. D. Ryabov, K.-W. Schramm and T. J. Collins, *Green Chem.*, 2007, **9**, 49–57.
326 D. A. Mitchell, A. D. Ryabov, S. Kundu, A. Chanda and T. J. Collins, *J. Coord. Chem.*, 2010, **63**, 2605–2618.
327 M. A. DeNardo, M. R. Mills, A. D. Ryabov and T. J. Collins, *J. Am. Chem. Soc.*, 2016, **138**, 2933–2936.
328 *TAML® Catalytic Oxidant Activators in the Pulp and Paper Industry*, ed. T. J. Collins, C. P. Horwitz, A. D. Ryabov, L. D. Vuocolo, S. Sen Gupta, A. Ghosh, N. L. Fattaleh, Y. Hangun, B. Steinhoff, C. A. Noser, E. Beach, D. Prasuhn Jr., T. Stuthridge, K. G. Wingate, J. Hall, L. J. Wright, I. Suckling and R. W. Allison, American Chemical Society, Washington, DC, 2002.
329 N. W. Shappell, M. A. Vrabel, P. J. Madsen, G. Harrington, L. O. Billey, H. Hakk, G. L. Larsen, E. S. Beach, C. P. Horwitz, K. Ro, P. G. Hunt and T. J. Collins, *Environ. Sci. Technol.*, 2008, **42**, 1296–1300.
330 J. L. Chen, S. Ravindran, S. Swift, L. J. Wright and N. Singhal, *Water Res.*, 2012, **46**, 6309–6318.
331 A. D. Ryabov, *Adv. Inorg. Chem.*, 2013, **65**, 118–163.
332 R. T. Malecky, E. S. Beach, C. P. Horwitz and T. J. Collins, Presented in part at the 232nd ACS National Meeting, San Francisco, CA, 2006.
333 N. R. Campbell, *Proc. R. Soc. London, Ser. B*, 1940, **129**, 528–538.
334 E. E. Reid and E. Wilson, *J. Am. Chem. Soc.*, 1944, **66**, 967–969.
335 T. Hirano, Y. Honda, T. Watanabe and M. Kuwahara, *Biosci. Biotechnol., Biochem.*, 2000, **64**, 1958–1962.
336 T. T. Schug, R. Abagyan, B. Blumberg, T. J. Collins, D. Crews, P. L. DeFur, S. M. Dickerson, T. M. Edwards, A. C. Gore, L. J. Guillette, T. Hayes, J. J. Heindel, A. Moores, H. B. Patisaul, T. L. Tal, K. A. Thayer, L. N. Vandenberg, J. Warner, C. S. Watson, F. S. v. Saal, R. T. Zoeller, K. P. O'Brien and J. P. Myers, *Green Chem.*, 2013, **15**, 181–198.
337 P. George, *Biochem. J.*, 1953, **55**, 220–230.
338 H. A. Balsiger, R. de la Torre, W.-Y. Lee and M. B. Cox, *Sci. Total Environ.*, 2010, **408**, 1422–1429.
339 E. J. Routledge and J. P. Sumpter, *Environ. Toxicol. Chem.*, 1996, **15**, 241–248.
340 L. Truong, D. M. Reif, L. St. Mary, M. C. Geier, H. D. Truong and R. L. Tanguay, *Toxicol. Sci.*, 2014, **137**, 212–233.
341 A. Ghosh, A. D. Ryabov, S. M. Mayer, D. C. Horner, D. E. Prasuhn, S. Sen Gupta, L. Vuocolo, C. Culver, M. P. Hendrich, C. E. F. Rickard, R. E. Norman, C. P. Horwitz and T. J. Collins, *J. Am. Chem. Soc.*, 2003, **125**, 12378–12379.
342 M. A. Mendez, M. F. Suarez and M. T. Cortes, *J. Electroanal. Chem.*, 2006, **590**, 181–189.
343 I. L. Kogan and K. Yakushi, *Electrochim. Acta*, 1998, **43**, 2053–2060.
344 D.-L. Popescu, M. Vrabel, A. Brausam, P. Madsen, G. Lente, I. Fabian, A. D. Ryabov, R. van Eldik and T. J. Collins, *Inorg. Chem.*, 2010, **49**, 11439–11448.
345 M. Emelianenko, D. Torrejon, M. DeNardo, A. Socolofsky, A. Ryabov and T. Collins, *J. Math. Chem.*, 2014, **52**, 1460–1476.
346 M. A. DeNardo, *Ph.D. Dissertation*, Carnegie Mellon, March 26, 2016.
347 J. S. Dordick, M. A. Marletta and A. M. Klibanov, *Biotechnol. Bioeng.*, 1987, **30**, 31–36.
348 M. Reihmann and H. Ritter, *Adv. Polym. Sci.*, 2006, **194**, 1–49.
349 S. Kobayashi, H. Kurioka and H. Uyama, *Macromol. Rapid Commun.*, 1996, **17**, 503–508.
350 H. Sakuyama, Y. Endo, K. Fujimoto and Y. Hatano, *J. Biosci. Bioeng.*, 2003, **96**, 227–231.
351 S. Kobayashi, H. Uyama, T. Ushiwata, T. Uchiyama, J. Sugihara and H. Kurioka, *Macromol. Chem. Phys.*, 1998, **199**, 777–782.
352 H. Uyama, N. Maruichi, H. Tonami and S. Kobayashi, *Biomacromolecules*, 2002, **3**, 187–193.
353 J. Kulys, R. Vidziunaite, A. Ziemys and I. Bratkovskaja, *Biologija*, 2007, **53**, 40–44.
354 Y. H. Kim, E. S. An, S. Y. Park, J.-O. Lee, J. H. Kim and B. K. Song, *J. Mol. Catal. B: Enzym.*, 2007, **44**, 149–154.
355 S. Arulmozhiraja, M. L. Coote, Y. Kitahara, M. Juhász and T. Fujii, *J. Phys. Chem. A*, 2011, **115**, 4874–4881.
356 B. Kolvenbach, N. Schlaich, Z. Raoui, J. Prell, S. Zühlke, A. Schäffer, F. P. Guengerich and P. F. X. Corvini, *Appl. Environ. Microbiol.*, 2007, **73**, 4776–4784.
357 W. Zhang, K. Yin and L. Chen, *Appl. Microbiol. Biotechnol.*, 2013, **97**, 5681–5689.
358 T. Fukuda, H. Uchida, Y. Takashima, T. Uwajima, T. Kawabata and M. Suzuki, *Biochem. Biophys. Res. Commun.*, 2001, **284**, 704–706.
359 N. Grassie, M. I. Guy and N. H. Tennent, *Polym. Degrad. Stab.*, 1985, **12**, 65–91.

360 J.-H. Kim, P.-K. Park, C.-H. Lee, H.-H. Kwon and S. Lee, *J. Membr. Sci.*, 2008, **312**, 66–75.
361 S. H. Dai, C. Y. Lin, D. V. Rao, F. A. Stuber, P. S. Carleton and H. Ulrich, *J. Org. Chem.*, 1985, **50**, 1722–1725.
362 W.-F. Chen, H.-Y. Lin and S. A. Dai, *Org. Lett.*, 2004, **6**, 2341–2343.
363 R. W. Murray and H. Gu, *J. Org. Chem.*, 1995, **60**, 5673–5677.
364 E. C. Dodds and W. Lawson, *Proc. R. Soc. London, Ser. B*, 1938, **125**, 222–232.
365 J. Chen, Y. Xiao, Z. Gai, R. Li, Z. Zhu, C. Bai, R. L. Tanguay, X. Xu, C. Huang and Q. Dong, *Aquat. Toxicol.*, 2015, **169**, 204–214.
366 P. Sohoni, C. R. Tyler, K. Hurd, J. Caunter, M. Hetheridge, T. Williams, C. Woods, M. Evans, R. Toy, M. Gargas and J. P. Sumpter, *Environ. Sci. Technol.*, 2001, **35**, 2917–2925.
367 F. Lahnsteiner, B. Berger, M. Kletzl and T. Weismann, *Aquat. Toxicol.*, 2005, **75**, 213–224.
368 A. Hatef, S. M. H. Alavi, A. Abdulfatah, P. Fontaine, M. Rodina and O. Linhart, *Ecotoxicol. Environ. Saf.*, 2012, **76**, 56–62.
369 H. Hayashi, A. Nishimoto, N. Oshima and S. Iwamuro, *J. Toxicol. Sci.*, 2007, **32**, 91–96.
370 D. L. Villeneuve, N. Garcia-Reyero, B. L. Escalon, K. M. Jensen, J. E. Cavallin, E. A. Makynen, E. J. Durhan, M. D. Kahl, L. M. Thomas, E. J. Perkins and G. T. Ankley, *Environ. Sci. Technol.*, 2012, **46**, 51–59.
371 S. Liu, F. Qin, H. Wang, T. Wu, Y. Zhang, Y. Zheng, M. Li and Z. Wang, *Aquat. Toxicol.*, 2012, **122–123**, 19–27.
372 F. Qin, L. Wang, X. Wang, S. Liu, P. Xu, H. Wang, T. Wu, Y. Zhang, Y. Zheng, M. Li, X. Zhang, C. Yuan, G. Hu and Z. Wang, *Comp. Biochem. Physiol., Part C: Pharmacol., Toxicol. Endocrinol.*, 2013, **157**, 192–202.
373 C. D. Metcalfe, T. L. Metcalfe, Y. Kiparissis, B. G. Koenig, C. Khan, R. J. Hughes, T. R. Croley, R. E. March and T. Potter, *Environ. Toxicol. Chem.*, 2001, **20**, 297–308.
374 K. S. Saili, M. M. Corvi, D. N. Weber, A. U. Patel, S. R. Das, J. Przybyla, K. A. Anderson and R. L. Tanguay, *Toxicology*, 2012, **291**, 83–92.
375 W. Lee, C.-W. Kang, C.-K. Su, K. Okubo and Y. Nagahama, *Chemosphere*, 2012, **88**, 945–952.
376 J. Wang, X. Liu, H. Wang, T. Wu, X. Hu, F. Qin and Z. Wang, *Comp. Biochem. Physiol., Part C: Pharmacol., Toxicol. Endocrinol.*, 2010, **152**, 313–320.
377 E. Chung, M. C. Genco, L. Megrelis and J. V. Ruderman, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 17732–17737.
378 S. H. Lam, M. M. Hlaing, X. Zhang, C. Yan, Z. Duan, L. Zhu, C. Y. Ung, S. Mathavan, C. N. Ong and Z. Gong, *PLoS One*, 2011, **6**, e28273.
379 Y. Gibert, S. Sassi-Messai, J.-B. Fini, L. Bernard, D. Zalko, J.-P. Cravedi, P. Balaguer, M. Andersson-Lendahl, B. Demeneix and V. Laudet, *BMC Dev. Biol.*, 2011, **11**, 1–18.
380 T. R. Baker, R. E. Peterson and W. Heideman, *Toxicol. Sci.*, 2013, **135**, 241–250.
381 M. D. Anway and M. K. Skinner, *Endocrinology*, 2006, **147**, s43–s49.
382 D. Crews, A. C. Gore, T. S. Hsu, N. L. Dangleben, M. Spinetta, T. Schallert, M. D. Anway and M. K. Skinner, *Proc. Natl. Acad. Sci. U. S. A.*, 2007, **104**, 5942–5946.
383 M. Shelby, *NTP CERHR MON*, 2008, **22**, v, vii–ix, 1–64 passim.
384 D. Melzer, N. E. Rice, C. Lewis, W. E. Henley and T. S. Galloway, *PLoS One*, 2010, **5**, e8673.
385 D. Li, Z. Zhou, D. Qing, Y. He, T. Wu, M. Miao, J. Wang, X. Weng, J. R. Ferber, L. J. Herrinton, Q. Zhu, E. Gao, H. Checkoway and W. Yuan, *Hum. Reprod.*, 2010, **25**, 519–527.
386 D.-K. Li, Z. Zhou, M. Miao, Y. He, J. Wang, J. Ferber, L. J. Herrinton, E. Gao and W. Yuan, *Fertil. Steril.*, 2011, **95**(2), 625–630.e4.
387 D.-K. Li, Z. Zhou, M. Miao, Y. He, D. Qing, T. Wu, J. Wang, X. Weng, J. Ferber, L. J. Herrinton, Q. Zhu, E. Gao and W. Yuan, *J. Androl.*, 2010, **31**, 500–506.
388 D.-K. Li, M. Miao, Z. Zhou, C. Wu, H. Shi, X. Liu, S. Wang and W. Yuan, *PLoS One*, 2013, **8**, e65399.
389 J. R. Rochester, *Reprod. Toxicol.*, 2013, **42**, 132–155.
390 H. Watanabe, R. Adachi, K. Kusui, A. Hirayama, T. Kasahara and K. Suzuki, *Int. Immunopharmacol.*, 2003, **3**, 1601–1608.
391 G. S. Prins, W.-Y. Hu, G.-B. Shi, D.-P. Hu, S. Majumdar, G. Li, K. Huang, J. L. Nelles, S.-M. Ho, C. L. Walker, A. Kajdacsy-Balla and R. B. van Breemen, *Endocrinology*, 2014, **155**, 805–817.
392 W.-Y. Hu, G.-B. Shi, H.-M. Lam, D.-P. Hu, S.-M. Ho, I. C. Madueke, A. Kajdacsy-Balla and G. S. Prins, *Endocrinology*, 2011, **152**, 2150–2163.
393 S. Soriano, P. Alonso-Magdalena, M. García-Arévalo, A. Novials, S. J. Muhammed, A. Salehi, J.-A. Gustafsson, I. Quesada and A. Nadal, *PLoS One*, 2012, **7**, e31109.
394 E. Hugo, T. Brandebourg, J. Woo, J. Loftus, J. Alexander and N. Ben-Jonathan, *Environ. Health Perspect.*, 2008, **116**, 1642–1647.
395 Y. B. Wetherill, C. E. Petre, K. R. Monk, A. Puga and K. E. Knudsen, *Mol. Cancer Ther.*, 2002, **1**, 515–524.
396 R. Steinmetz, N. G. Brown, D. L. Allen, R. M. Bigsby and N. Ben-Jonathan, *Endocrinology*, 1997, **138**, 1780–1786.
397 S. F. Arnold, D. M. Klotz, B. M. Collins, P. M. Vonier, L. J. Guillette and J. A. McLachlan, *Science*, 1996, **272**, 1489–1492.
398 S. i. Yoshihara, M. Makishima, N. Suzuki and S. Ohta, *Toxicol. Sci.*, 2001, **62**, 221–227.
399 A. L. Herbst, H. Ulfelder and D. C. Poskanzer, *N. Engl. J. Med.*, 1971, **284**, 878–881.
400 K. Okuda, M. Takiguchi and S. i. Yoshihara, *Toxicol. Lett.*, 2010, **197**, 7–11.
401 M. E. Baker and C. Chandsawangbhuwana, *PLoS One*, 2012, **7**, e46078.
402 R. B. Stebbins and E. W. Blanchard, *Endocrinology*, 1945, **36**, 305–312.

403 H. Ishibashi, N. Watanabe, N. Matsumura, M. Hirano, Y. Nagao, H. Shiratsuchi, S. Kohra, S.-i. Yoshihara and K. Arizono, *Life Sci.*, 2005, **77**, 2643–2655.
404 A. Yamaguchi, H. Ishibashi, S. Kohra, K. Arizono and N. Tominaga, *Aquat. Toxicol.*, 2005, **72**, 239–249.
405 S.-H. Liu, C.-C. Su, K.-I. Lee and Y.-W. Chen, *Sci. Rep.*, 2016, **6**, 39254.
406 H. Miyakoda, M. Tabata, S. Onodera and K. Tkeda, *J. Health Sci.*, 1999, **45**, 318–323.
407 Y. Ikezuki, O. Tsutsumi, Y. Takai, Y. Kamei and Y. Taketani, *Hum. Reprod.*, 2002, **17**(11), 2839–2841.
408 G. Schönfelder, W. Wittfoht, H. Hopp, C. E. Talsness, M. Paul and I. Chahoud, *Environ. Health Perspect.*, 2002, **110**, A703–A707.
409 Y. J. Lee, H.-Y. Ryu, H.-K. Kim, C. S. Min, J. H. Lee, E. Kim, B. H. Nam, J. H. Park, J. Y. Jung, D. D. Jang, E. Y. Park, K.-H. Lee, J.-Y. Ma, H.-S. Won, M.-W. Im, J.-H. Leem, Y.-C. Hong and H.-S. Yoon, *Reprod. Toxicol.*, 2008, **25**, 413–419.
410 S. M. Engel, B. Levy, Z. Liu, D. Kaplan and M. S. Wolff, *Reprod. Toxicol.*, 2006, **21**, 110–112.
411 J. Matsumoto, H. Yokota and A. Yuasa, *Environ. Health Perspect.*, 2002, **110**, 193–196.
412 C. P. Strassburg, A. Strassburg, S. Kneip, A. Barut, R. H. Tukey, B. Rodeck and M. P. Manns, *Gut*, 2002, **50**, 259–265.
413 M. W. Coughtrie, B. Burchell, J. E. Leakey and R. Hume, *Mol. Pharmacol.*, 1988, **34**, 729–735.
414 G. M. Pacifici, M. Kubrich, L. Giuliani, M. de Vries and A. Rane, *Eur. J. Clin. Pharmacol.*, 1993, **44**, 259–264.
415 O. Tsutsumi, *J. Steroid Biochem. Mol. Biol.*, 2005, **93**, 325–330.
416 S.-M. Ho, W.-Y. Tang, J. Belmonte de Frausto and G. S. Prins, *Cancer Res.*, 2006, **66**, 5624–5632.
417 L. N. Vandenberg, M. V. Maffini, C. M. Schaeberle, A. A. Ucci, C. Sonnenschein, B. S. Rubin and A. M. Soto, *Reprod. Toxicol.*, 2008, **26**, 210–219.
418 L. Speroni, M. Voutilainen, M. L. Mikkola, S. A. Klager, C. M. Schaeberle, C. Sonnenschein and A. M. Soto, *Sci. Rep.*, 2017, **7**, 40806.
419 M. Kitada, T. Kamataki, K. Itahashi, T. Rikihisa and Y. Kanakubo, *J. Biol. Chem.*, 1987, **262**, 13534–13537.
420 A. Schecter, T. T. Schug, S. A. Vogel, L. N. Vandenberg, J. Braun, R. Hauser, J. A. Taylor, F. S. v. Saal and J. J. Heindel, *Dioxins and Health: Including Other Persistent Organic Pollutants and Endocrine Disruptors*, Wiley & Sons, New York, 2012.
421 *Proposed Notice Requiring the Preparation and Implementation of Pollution Prevention Plans with Respect to Bisphenol A In Industrial Effluents*, Canada Gazette, Public Works and Government Services Canada, Ottawa, Canada, 2010, http://publications.gc.ca/gazette/archives/p1/2010/2010-10-16/pdf/g1-14442.pdf .
422 F. G. Doherty, *Water Qual. Res. J. Can.*, 2001, **36**, 475–518.
423 F. Manservisi, C. B. Marquillas, A. Buscaroli, J. Huff, M. Lauriola, D. Mandrioli, M. Manservigi, S. Panzacchi, E. K. Silbergeld and F. Belpoggi, *Environ. Health Perspect.*, 2017, **125**, 289–295.