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,† Soumen Kundi, b Alexander D. Ryabov,*,b Evan S. Beach,† c Robert L. Tanguay,† c L. James Wright,*,d Naresh Singhal,† a and Terrence J. Collins‡ a

Designing technologies that mitigate the low-dose adverse effects of exposures to large-volume, everyday-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/H2O2 purification of 1a contaminated waters. TAML/H2O2 catalysis readily oxidizes BPA (1a) and the ring-tetramethyl (1b), tetrachloro (1c), and tetrabromo (1d)-substituted derivatives. At pH 8.5, TAML/H2O2 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/H2O2 (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/H2O2 treated, catalase quenched, and filtered oxidation solutions show elimination of 1a oestrogenicity. Zebrafish developmental assays of TAML/H2O2 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/H2O2 oxidations of 1a–d are fast with second order rate constants for the substrate oxidation process (k1 values) of (0.57–8) × 107 M−1 s−1. The 1a oxidation gives CO and CO2 (~78%), acetone (~25%) and formate (~1%). In striking contrast with pH 8.5 treatment, no oligomers were detected. TAML/H2O2 (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 pK values of 1a were estimated by fitting the pH dependence of the UV-vis spectra (pK = 9.4 ± 0.3; pK = 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, k1 values and the redox potentials of 1a–d as determined by differential pulse voltammetry in CH3CN is consistent with rate-limiting, electron transfer from the dianionic...
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/H₂O₂ treated 1a solutions showed significantly reduced toxicity. The facility and high efficiency by which TAML/H₂O₂ 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,11–19 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),1,5,13,20,22,23 which can alter the functioning of cellular proteins at sub-picomolar to nanomolar concentrations.13,24 Oestrogens regulate development25–27 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 breast32 and prostate cancer,33,34 therapeutics. In addition to acting as an oestrogen, 1a can act as a thyroid hormone,15,36 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.20,23–31,38–44 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

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 resins18 (Fig. 1), including those used to line food and water containers such as metal cans,49,50 metal and concrete drinking water pipes51,52 and residential water storage tanks.52,53 BPA is also added to phenoxy,54 polyacrylate,55,56 poly-arylate,57,58 polyetherimide,58 polyester,55,56,58,59 polyester-styrene,55 and polysulfone54,56,58,59 plastic and resins,34 and rubber, polyethylene tetraphthalate,13,54,55,59 and polyvinyl chloride (PVC) products where it can function as a stabilizer,54,60,61 antioxidant62,63 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.\textsuperscript{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,\textsuperscript{6,66} 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.\textsuperscript{68,69} Aqueous 1a concentrations of 1.98–139 µg L\textsuperscript{−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.\textsuperscript{60,67} Room temperature, 24-hour exposure of pure water to PVC hoses resulted in leaching of 4–1730 µg L\textsuperscript{−1} of 1a.\textsuperscript{67,70} Contamination also occurred upon passage through the tube and increased from 8.7–558 µg L\textsuperscript{−1} as the water residence time increased from 0–24 hours.\textsuperscript{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\textsuperscript{−1} day\textsuperscript{−1}, respectively—the amount of 1a leached is less than that from PVC hoses.\textsuperscript{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.\textsuperscript{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\textsubscript{2}O\textsubscript{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\textsuperscript{110–112} and sediments.\textsuperscript{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,\textsuperscript{74,114} 1a oxidation by radical oxygen species is slower in seawater than in control water,\textsuperscript{71} and marine bacteria strains have been found to degrade 1a much more slowly than freshwater strains.\textsuperscript{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.\textsuperscript{110,111,116}

The reported sediment contamination levels exceed those of both sea and fresh water.\textsuperscript{65} 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.\textsuperscript{117} Since 1a degradation is slower under anaerobic than aerobic conditions,\textsuperscript{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,\textsuperscript{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.\textsuperscript{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\textsuperscript{−1} or 1.3–19 nM).\textsuperscript{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\textsuperscript{−1} or 23 nM, range: 0.3–149 µg L\textsuperscript{−1} or 1.3–653 nM).\textsuperscript{121} Concentrations have been found in human colostrum (total 1a, all samples, 1–7 µg L\textsuperscript{−1}, mean of 3.41 µg L\textsuperscript{−1})\textsuperscript{122} and breast milk (total 1a, 90% of samples, <0.3–6.3 µg L\textsuperscript{−1}, mean of 1.3 µg L\textsuperscript{−1}).\textsuperscript{123} Breast milk concentrations were found to rise from 6.2 µg L\textsuperscript{−1} to ca. 30 µg L\textsuperscript{−1} one hour after consumption of a canned coffee drink containing 37.4 µg,\textsuperscript{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\textsuperscript{−1},\textsuperscript{125} Atibaia River watershed of São Paulo, Brazil: weighted average of 4.6 and maximum of 13 µg L\textsuperscript{−1};\textsuperscript{126} Dongguan watershed of China: average of 6.5 and maximum of 56 µg L\textsuperscript{−1};\textsuperscript{127} Nagara River of Japan: average of 4.8 and maximum of 22.2 µg L\textsuperscript{−1};\textsuperscript{117} and Portugal: 0.07–4 µg L\textsuperscript{−1}).\textsuperscript{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.\textsuperscript{78,79} While municipal drinking water itself is not typically considered a major source of 1a (France 2011: <9–50 ng L\textsuperscript{−1};\textsuperscript{129} Germany 2000: 0.003–2 ng L\textsuperscript{−1};\textsuperscript{130} Malaysia 2009: 3.5–59.8 ng L\textsuperscript{−1};\textsuperscript{131} Spain 2003: <5–25 ng L\textsuperscript{−1}),\textsuperscript{113} significantly higher drinking water concentrations have been reported (Nigeria 2015: 109.00–882.50 µg L\textsuperscript{−1}).\textsuperscript{131} Removal of 1a by conversion to transformation pro-
products,\textsuperscript{139} including \textit{Lev (Fig. 1)},\textsuperscript{134,135} during disinfection by chlorination prior to release may contribute to the reported, low drinking water \textit{a} concentrations. The potential human health and environmental impacts of exposure to \textit{a} chlorination products are briefly discussed later in this work. The higher reported \textit{a} drinking water concentrations derive from both a higher initial \textit{a} concentration and contributions from plastic storage container leachate.\textsuperscript{131} Passage through tap mounted filter devices,\textsuperscript{131} pipes lined with epoxy resin, or poly-carbonate or PVC tubing can also raise \textit{a} concentrations.\textsuperscript{129} Ingestion of leachate\textsuperscript{10,136} from polycarbonate,\textsuperscript{137,138} epoxy,\textsuperscript{53,62,136} and organosol\textsuperscript{12,139} resins such as those made from bisphenol A diglycidyl ether (BADGE, Fig. 1), and \textit{a} stabilizers and antioxidants\textsuperscript{62,63} in, for example, food contact papers,\textsuperscript{140} PVC stretch films,\textsuperscript{141} dental sealants,\textsuperscript{80,101,142} and food and drink containers\textsuperscript{49,50,52,63,139,152,156} including commercial polycarbonate containers used for microwave ovens,\textsuperscript{69} adult\textsuperscript{131,152} and baby\textsuperscript{52,133,157} water bottles and cans\textsuperscript{50,52,163} is the most authoritatively documented route of human \textit{a} exposure.

Canned goods are perhaps the most well-studied source of dietary \textit{a}. Globally, contamination with \textit{a} has been detected in canned beets,\textsuperscript{154} decaffeinated and non-decaffeinated coffees,\textsuperscript{162,164} soft drinks,\textsuperscript{165,166} including diet and regular ginger ales, diet and regular root beers,\textsuperscript{165} diet and regular colas,\textsuperscript{154,165} energy drinks,\textsuperscript{154,165} orange and lemon soft drinks,\textsuperscript{154} flavoured and unflavoured soda waters,\textsuperscript{165} teas,\textsuperscript{165} and tonic waters,\textsuperscript{165} infant\textsuperscript{167,168} and follow up formulas,\textsuperscript{170} the liquid phases of canned artichokes, green beans, corn, mushrooms, peas, and mixed vegetables,\textsuperscript{50} the homogenized liquid and solid contents of canned fruit products including coconut cream,\textsuperscript{154,171} coconut milk,\textsuperscript{136} lychees, mangoes,\textsuperscript{154} olives,\textsuperscript{171} peaches, light pineapples,\textsuperscript{154} tomatoes,\textsuperscript{63,155,156,171} tomato juice\textsuperscript{156} and tomato paste,\textsuperscript{172} and fruit pieces and cocktails,\textsuperscript{53} the homogenized liquid and solid contents of canned vegetable products including asparagus,\textsuperscript{156} baked beans in tomato sauce, green beans,\textsuperscript{171} beetroot,\textsuperscript{171} carrots,\textsuperscript{63} corn,\textsuperscript{63,171,172} mount elephants, mushrooms,\textsuperscript{156} peas,\textsuperscript{53,171} jalapeño peppers,\textsuperscript{153} potatoes,\textsuperscript{63,171} and goulash,\textsuperscript{154} the homogenized liquid and solid contents of canned soups,\textsuperscript{171,172} including cream of chicken, chicken and white wine,\textsuperscript{63} potato,\textsuperscript{154} tomato,\textsuperscript{63} and Tom Kha,\textsuperscript{154} the homogenized liquid and solid contents of canned sauces,\textsuperscript{171} of many varieties including demi-glace, fond de volaille, gratin, meat, tomato, and white,\textsuperscript{156} the homogenized liquid and solid contents of canned pastas in tomato sauce,\textsuperscript{63} the homogenized liquid and solid contents of canned seafood including Japanese sand lance, mackerel,\textsuperscript{156} pilchards in tomato sauce,\textsuperscript{63} salmon,\textsuperscript{63,156,171} sardine,\textsuperscript{156} sardine in tomato sauce,\textsuperscript{63} shrimp,\textsuperscript{156} tuna,\textsuperscript{156,171,172} and fish and vegetable mixtures,\textsuperscript{156} the homogenized liquid and solid contents of canned meats,\textsuperscript{171} including chicken, corned beef, fish balls, ham, hot dogs, and pork,\textsuperscript{63} the homogenized liquid and solid contents of canned quail eggs,\textsuperscript{156} the homogenized liquid and solid contents of desserts including evaporated milk,\textsuperscript{53,173} and creamed rice,\textsuperscript{63} the solids of canned crushed tomatoes, young peas,\textsuperscript{154} corn,\textsuperscript{154,174} haricot beans, red kidney beans, lentils,\textsuperscript{154} mushrooms,\textsuperscript{174} tuna in oil, and sardines in oil,\textsuperscript{154} mackerel fillet in tomato sauce, and canned dinners.\textsuperscript{166} Contamination of vegetable solids has been found to be greater than that of the liquids.\textsuperscript{174}

Alone, the estimated child and adult dietary intakes (0.008–14.7 μg kg\(^{-1}\) day\(^{-1}\))\textsuperscript{162} are unlikely to account for the concentrations observed in human bloodstreams.\textsuperscript{79} The human oral dosage necessary to maintain the average unconjugated \textit{a} 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\(^{-1}\).\textsuperscript{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\(^{-1}\).\textsuperscript{175} Therefore, alternate routes of exposure which obviate the first pass metabolism of the liver that greatly reduces blood concentrations of unconjugated \textit{a},\textsuperscript{79} including dermal uptake, which increases when skin is wet and/or greasy,\textsuperscript{176,177} and sublingual absorption\textsuperscript{78,79} are thought to contribute to human blood concentrations of \textit{a}. For example, the handling of thermal receipt papers, which are coated in amounts of unbound \textit{a} that have been found to be at least one thousand times greater than that of food can epoxy linings,\textsuperscript{178} is the most well-known route of dermal exposure.\textsuperscript{140,177,179–182}

Given the myriad of products into which \textit{a} 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 \textit{a}. While not directly proven to raise blood concentrations of \textit{a}, it is reasonable to expect additional exposures from, \textit{inter alia}, indoor and outdoor air,\textsuperscript{183–186} indoor dust,\textsuperscript{183–185,187–189} 5 gallon water carboys,\textsuperscript{157} polyethylene terephthalate,\textsuperscript{13,132,190} and polycarbonate water bottles,\textsuperscript{129} drinking water generators,\textsuperscript{52} and pipes,\textsuperscript{51} water main\textsuperscript{55} and tap\textsuperscript{131} filters, fungicides,\textsuperscript{54,55,59} randomly selected fresh foods including fresh cherries, courgettes, eggplants, medlars, oranges, peaches, peppers, and tomatoes,\textsuperscript{191} white clams, crabs, blood cockles, fish, prawn, and squid,\textsuperscript{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,\textsuperscript{166} honey packaged in glass or plastic that was imported in epoxy-lined metal drums,\textsuperscript{192} baby food products in glass\textsuperscript{193} and high-density polyethylene plastic,\textsuperscript{168} jars with metal lids, solid\textsuperscript{185} and liquid foods served at day care centers,\textsuperscript{183,184} baby teethers,\textsuperscript{194} breastpumps,\textsuperscript{52} children’s books and toys,\textsuperscript{52,195,196} cosmetics,\textsuperscript{197} training cups,\textsuperscript{157} dishwasher and laundry detergents,\textsuperscript{198} protective and general sporting equipment,\textsuperscript{52,79} inhaler housings, musical instrument mouthpieces,\textsuperscript{52} plastic plates and utensils,\textsuperscript{12,79,133} including those used at elementary schools,\textsuperscript{162} nail polish,\textsuperscript{55,198} pillow protectors,\textsuperscript{198} outdoor play area soil,\textsuperscript{181} artificial teeth,\textsuperscript{55} hand, hard floor surface and food preparation surface wipes,\textsuperscript{184} personal care-hygiene pro-
products including cleansers, conditioner, shaving cream, lotions, shampoo, bar soap, sunscreen, toothbrushes, toothpaste, and face and body washes, 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, building materials including structural adhesives and fillers, coatings, carpentry covers, flooring, architectural, conservatory, greenhouses, and bus stop shelter glazings, grouting, mortars, concrete reinforcement, sheets for roofing, ceiling tiles, and road and train track noise reduction walls, the casings of cameras, computers, copiers, monitors, phones, pens, steam irons, telephones, suitcases, and TVs, paper currencies, CDs, DVDs, hair dryers, cigarette filters, contact lens holders, eyeglass frames, lenses, pens, recycled cellulose fiber (RCF) products including the food contact surfaces of confectionary, fried chicken, fried potato, pizza, sandwich, and general food storage boxes as well as noodle cups, virgin paper products including coffee filters, cooking papers, cups, dishes, napkins, tea bags, tissues, and fried chicken wrapping paper, the epoxy paints, coatings and composites of aircraft, car, boat, and DIY repair adhesives 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 hair sprays, caps, closures and crown corks, general and sea containers, cookers, deckings, 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.e. connectors, dialysers, medical packaging film, blood oxygenators and sample reservoirs, cardiomyocytes, respirators, single use surgical tools, and medical tubing, the polycarbonate plastics, resin linings, and printed circuit boards of electronic products, 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, refrigerator crispers, drawers, electrical kettles, coffee makers, microwaves, mixers, and food processors, and PVC products including synthetic leather, in, for example, seating materials and clothing, shower curtains, and cord coverings. It is important to note that the concentrations found can be high. For example, a Nigerian study recorded in the occurrences above reported a 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.

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. 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.” 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. This value was chosen because it is an order of magnitude greater than the 2009 partial no effect concentration (PNEC) of 1a—it has been argued that the PNEC for 1a in surface waters should be lowered to 0.06 μg L⁻¹ 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. 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 13% 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). Landfilled postconsumer goods release 1a Consequently, water that has contacted waste, known as landfill leachate, has been reported to be a major source of 1a in the environment (Germany 2002: 4200–25 000 μg L⁻¹, average of 14 067 μg L⁻¹, Germany 2003: ca. 500–5000 μg L⁻¹, Japan 1999: ca. 500–7500 μg L⁻¹, Japan 1996: <0.5–1720 μg L⁻¹, median of 269 μg L⁻¹, Norway 2015: 0.7–200 μg L⁻¹, average of 66.5 μg L⁻¹, Philippines 2003: ca. 9000 μg L⁻¹, and Sweden 2000: 4–136 μg L⁻¹). These mixed pollutant streams containing 1a
may or may not be treated based on local judgments of the need for such.24 Treatments often include recycling through the landfill, on-site biological treatment,90 coagulation, filtration, and/or activated carbon adsorption,34,89 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 FeCl₃ 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 undisposed 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 releases 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 (NH₃ → NO₃⁻). The third engaged a denitrifying culture (NO₃⁻ → N₂). 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 release 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 O₃ 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⁻¹229 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)211 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 itself62 and the sink/float/heavy media separation slurries, chemical etchants, detinning, and chemical delaquering 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.202,212 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⁻¹229 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).224 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.234,235 Primarily, this removal occurs through sorption to primary sludge and sorption to activated sludge which may or may not be followed by biological degradation.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.5,55,98,216,239–243 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, these can come at the expense of increased sludge contamination.

The contaminated sludge generated in biological treatment can also become a source of \(1\). Sludge concentrations of \(0.10\)–\(3.2 \times 10^7 \, \mu g \, kg^{-1}\) 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. 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 \(7.18 \times 10^6\) dry US tons of sewage sludge solids, 55% \((3.95 \times 10^6\) tons) of which was land applied,250 and in 2005, the EU-27 countries produced ca. \(10.96 \times 10^6\) 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 release to the environment 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 pasturizations amended with sewage containing multiple EDs.257,258,259 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 \(1\) 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 \(1\) detected in fresh produce.194 Soil \(1\) can partition into soil water93 which, in turn, can result in contamination of leafy vegetables,238,268 root crops238 and cereal grains.238 Unfortunately, while never applying sewage sludge or only applying decontaminated sewage sludge would limit soil concentrations of \(1\), this alone cannot ensure \(1\)-free soil.

Ongoing global deposition from ubiquitous contamination of the atmosphere and irrigation with treated and untreated contaminated water also contribute to soil concentrations of \(1\).70,268 Sources of atmospheric aerosol concentrations of \(1\) include volatilisation during processing, handling and transportation of \(1\) (at least 109 metric tons per year)231; 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 shredders226 and landfills226 For example, \(1\) 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, isopropyl 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 \(1\)-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 \(1\) 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 \(1\).276,277 From \(300–340\) °C, thermal degradation begins and \(1\) is a major product released along with smaller amounts of isopropylphenol, isopropylphenol and phenol.278 Up to 500 °C, there is very little decomposition of the \(1\) moiety.278 From \(500–600\) °C, arylalkyl ether bonds are further cleaved and \(1\) remains a major product released.276,277 At \(>600\) °C, the release of high boiling pyrolysates with epoxide end groups decreases markedly,279 presumably giving a more \(1\)-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 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 or may progressively rise to ca. \(540\) °C.280 The furnace temperatures must be maintained below \(566\) °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 \(1\). These then may or may not be treated with activated charcoal281 and/or lime or calcium carbonate282 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 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 \(1\) in excess of \(1.75\) \(\mu g \, L^{-1}\), which are often discharged to surface waters, have been reported (Austria 2000: <\(0.5–2.5\) \(\mu g \, L^{-1}\), mean of \(1.5 \, \mu g \, L^{-1}\);229 Canada 2004: 0.01–17.3 \(\mu g \, L^{-1}\);233 EU 2008: 3.13–45 \(\mu g \, L^{-1}\);284 2008: <\(0.02–7.6 \, \mu g \, L^{-1}\), weighted average of 0.32 \(\mu g \, L^{-1}\);231 US 1999: <\(0.01–2.7 \, \mu g \, L^{-1}\).285 While these alone are cause for concern, of perhaps greater concern are the by-products that can be formed at landfill leachate135 and wastewater286 treatment facilities if effluents are disinfected by chlorination prior to release.
These disinfection by-products can include mono- and poly-chlorinated forms of 1a including the tetra-chlorinated 1c. 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, 247 ERα, 24-fold greater activity than the untreated 1a solution was observed. The mixtures also induced β-galactosidase activity in a yeast two-hybrid system employing human ERα. In addition, 2,2′,6-triCIBPA, 2,6-diCIBPA, 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). In addition to being oestrogenic, the multiply chlorinated forms of 1a are more resistant to activated sludge treatment than 1a. Notably, 2,2′,6-triCIBPA only undergoes very slow degradation while 2,2′,6-triCIBPA and 1c are not degraded. Thus, in addition to degradation resulting from the use of 1c in flame retardants and as an epoxy intermediate, chlorination of 1a-containing waters may contribute to the 1c concentrations which have been detected in sewage sludge, river water and sediment.

Further treatment of WWTP effluent with powdered activated carbon (PAC) or ozone has been advanced to enhance removal of MPs from wastewater. The energy and resource demands of PAC treatment followed by sand filtration (PAC-SF) to retain the PAC and ozone are significant and similar. 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. 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. 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. BPA is readily degraded by ozone. For example, treatment of 10 045 μg L⁻¹ 1a in pH 6.0 lab water with ca. 0.1 mg L⁻¹ O₁ (4.05 mg O₃ per min) effects a >98% removal in 10 minutes with ca. 20% mineralization. The technical performance of ozone decreases as the water matrix becomes more complex and despite the extensive deployment of ozone in some countries, it is not widely used globally—the reasons vary by country. Where it is deployed, staff training, safety measures 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. 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. 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. 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. 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. However, incineration precludes the energetic gains and decreased production emissions of material reuse, generates emissions including carbon dioxide and can also generate PCDDs and PCDFs. Another recently suggested option for dealing with 1a contamination of feedstocks may involve establishing acceptable levels for 1a in recycled products. 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. 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. Effluents from the pulp thickening process have been reported to contain 196–10 300 μg L⁻¹ 1a. Washing of the pulp also generates contaminated solutions that are reused and may be bleached. If alkaline paper recycling plant pulping solutions are chlorine-bleached, chlorinated forms of 1a, including 1c, can be generated, as noted above. Primary treatment of these process waters transfers 95.9% of the influent 1a to the primary sludge. 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). 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).220 In most plants, this effluent is subjected to secondary treatment with activated sludge.206 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, landfill, 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 H2O2 oxidations. TAML catalysts and TAML/H2O2 processes appear to be environmentally benign based on a diversity of evidence307–310 and, as further shown here, are extremely simple to deploy. TAML/H2O2 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.3,329 Importantly, 2/H2O2 chemistry is comprised exclusively of biochemically common elements as a foundational strategy for avoiding toxicity.

The destructive potency toward micropollutants315,331 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/H2O2 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/H2O2 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/H2O2 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).99 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 oestrous 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 peroxidase335 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/H2O2 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/H2O2 at pH 11 and substantially mineralized and effectively eliminated from water, (ii) that 2/H2O2 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/H2O2 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 H2O2 were prepared daily from reagent grade H2O2 (30% w/w, Fluka) and standardized by measuring the absorbance at 230 nm (ε = 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 H2SO4 (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 NaHCO3 (5%, 100 mL) and combined with the solids. The resulting solution was dried over MgSO4, 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%). 1H NMR (300 MHz, d6-acetone, δ in Hz) δ 8.25 [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, (CH2)], 4.68–4.66 [m, 1H, (CH2)], 2.75 [d, J 0.8, 2H, CH2], 1.16 [s, 9H, CH3]. 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 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. 1H NMR (300 MHz, d6-acetone): δ 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, H2], 4.93 (quintet, J 1.5, 1H, H1), 2.09 [dd, J 1.5, 0.8, 3H, CH3]1H NMR (500 MHz, H2O + D2O) δ 7.41 [d, J 8.8, ArH], 6.75 [d, J 8.8, ArH], 2.11 [s, CH3]. 1H NMR (500 MHz, H2O + D2O) δ 7.41 [d, J 8.8, ArH], 6.75 [d, J 8.8, ArH], 2.11 [s, CH3]. 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 Packard 8453 Diode Array spectrophotometer equipped with a digital temperature controller RTE17 with a precision of ±1 °C. Stock solutions of 1 were prepared by dissolving solid (7.50 × 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 CH3OH) 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 deionized H2O) 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 k0 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 H2O2 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 H2O2 (4.0 × 10−3 M) in 1 min with shaking (5 min). 1H NMR spectra (500 MHz Bruker Avance 500) of the reaction mixtures were recorded for reaction mixtures containing 10% D2O and 1a (1.5 × 10−4 M), 2 (1.5 × 10−7 M) and H2O2 (7 × 10−5 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® A59-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 Na2CO3 (9 × 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 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® A59-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 Na2CO3 (9 × 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/H2O2 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 × 10−4 M), H2O2 (7.5 × 10−3 M) and 2 (1.5 ×
10⁻⁷ M). An excess (50-fold) of H₂O₂ relative to 1 was used (36 eq. H₂O₂ are required for mineralization). Reactions were initiated by addition with mixing of the H₂O₂ 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 × 10⁻⁶ M, [2] = (4.0–40) × 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 H₂O₂ (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 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. 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 chromatograph equipped with an Agilent 5975C inert XL MSD mass spectrometer with a Triple-Axis detector. ¹H 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 CD₃OD.

**Kinetic measurements**

Monitoring of pH 11 processes was performed at the wavelength of maximal absorbance (λ_max) of the corresponding phenol. Initial rates were calculated using the independently measured pH 11 extinction coefficients [ε/M⁻¹ cm⁻¹ (λ_max, nm)]; 1a [4.3 × 10⁴ (294)], 1b [3.6 × 10³ (294)], 1c [9.0 × 10⁴ (305)], and 1d [1.0 × 10⁴ (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 × 10⁻⁵ M) and H₂O₂ (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 H₂O₂. EM Quant strips were used to verify that all H₂O₂ 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. This method allowed for the screening of multiple samples in a short amount of time without the need for sample preparation. 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 H₂O₂ were normalized to 100% oestrogenic, which served as a reference point for subsequent screening tests during the reaction.

**Zebrafish development.** In order to further test the effects of 2/H₂O₂ treatment of BPA on aquatic organisms, we assessed changes in 22 morphological endpoints over the first 5 days of zebrafish development. All appropriate reaction controls were conducted.

**Results and discussion**

**Degradation at pH 8.5**

At pH 8.5, no degradation of 1a was detected over 1 h in the absence of H₂O₂, but 1a is vulnerable to H₂O₂ alone (36% degradation in 60 min). At pH 8.5 in the presence of 2 (2.4 × 10⁻⁸ M) and H₂O₂ (4.0 × 10⁻³ M), the concentration of 1a (4.38 × 10⁻⁵ M or 10 000 µg L⁻¹) decreased to 3.97 × 10⁻⁷ M (90 µg L⁻¹) within 30 min. Visually obvious differences were found between 2/H₂O₂ 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[H2O2] (4 × 10−9 M/4 × 10−6 M) treatment of 1a (4.4 × 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 C12H12O2 227.1067) and the other to a dimer of 1a apparently formed via oxidative coupling (m/z 453.2076 [2M – H]−; calcd for C16H24O4 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 trisilylated 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. 1H 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 δ 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 2H2O2 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 C12H12O2 227.1067), oxidatively coupled 1a dimers (m/z 453.2095 [2M – H]−; calcd for C24H24O4 453.2060) and trace trimers (m/z 679.3084 [3M – H]−; calcd for C24H24O6 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 C24H24O6 679.3054) with much smaller peaks for tetramers (m/z 905.4111 [4M – H]−; calcd for C36H36O8 905.4048) and pentamers (m/z 1131.4995 [5M – H]−; calcd for C48H48O10 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, 2H2O2 oxidations of 1 were studied by HPLC, total organic carbon (TOC) analysis, 1H NMR spectroscopy, and ion chromatography. In the absence of H2O2, degradation of 1a over 1 h is negligible at pH 12. At pH 11 in the presence of 2 (1.5 × 10−7 M) and H2O2 (7.5 × 10−3 M), the concentration of 1a (1.5 × 10−4 M or 34 244 μg L−1) decreased below the HPLC detection limit (1 × 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/H2O2 at pH 11, 1H 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, 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 δ 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 AAB′B′ pattern appeared (δ 6.65 and 7.15), as did three higher field (δ 1.62, 1.53, and 1.52) resonances.
These signals were no longer distinguishable from the baseline at 15 min. At pH 11, the final 2/H₂O₂-1a solution was transparent.

As in other TAML degradation studies of phenols and systems with likely phenolic intermediates, ion chromatography (IC) of the final 1b-d reaction solutions confirms the deep oxidation of 1. When 1a (1.5 × 10⁻⁴ M) was subjected to 2/H₂O₂ (1.5 × 10⁻⁷ M/7 × 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 × 10⁻⁴ M, [2] = 4.5 × 10⁻⁷ M, [H₂O₂] = 7 × 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 pH of 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 (A₂₉₅) 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 AH₂ ⇄ AH⁻ ⇄ A⁻²⁻ (AH₂ is 1a) in which [1a], is the total concentration of 1a, K_a and K_a2 are the first and the second dissociation constants for 1a, respectively, and ε_AH₂, ε_AH⁻, and ε_A are the extinction coefficients for the forms AH₂, AH⁻, and A⁻²⁻, respectively. The solid line in the inset is the calculated dependence of the absorbance on H⁺ which corresponds to the deprotonation sequence AH₂ ⇄ AH⁻ ⇄ A⁻²⁻. The variation in the absorbance at 295 nm (A₂₉₅) 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 AH₂ ⇄ AH⁻ ⇄ A⁻²⁻, respectively (Fig. 3).

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, 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.

\[
\frac{A_{1a}}{[1a]} = \frac{\varepsilon_{AH2}[H^+] + \varepsilon_{AH}[H^+] + \varepsilon_A}{[H^+]^2 + K_{A1}[H^+] + K_{A2}K_{A3}}
\]

Mechanism of pH 8.5 TAML-catalysed 1a oxidation

Oligomers such as those reported are commonly produced in enzyme-catalysed polymerizations of phenols including 1a. The initial step is often proposed to be a one-electron oxidation of the AH₂ or AH⁻ forms of 1a to produce phenolate radicals which can then couple to give higher molecular weight products. Our study mirrors the enzymatic results. There is little doubt that the oxidation starts with 1-electron oxidation of either AH₂ 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).

| R    | E/V (vs. SCE) |
|------|--------------|
| Me   | 0.181 ± 0.005|
| H    | 0.26 ± 0.01  |
| Br   | 0.37 ± 0.01  |
| Cl   | 0.41 ± 0.01  |

Table 1: Rate constants kₚₖ for the interaction of oxidized TAML with 1 (25 °C, pH 11) and the reduction potentials for 1 measured in MeCN (25 °C, μ = 0.1 M) using differential pulse voltammetry.
Fe^{III}-TAML + ROOH $\xrightarrow{k_{I}}$ (Oxidized TAML) \\
(Oxidized TAML) + Substrate $\xrightarrow{k_{II}}$ Fe^{III}-TAML + Primary Product \\
Primary Product $\xrightarrow{\text{fast}}$ Final Product(s)

Scheme 1 Stoichiometric mechanism of catalysis by TAML/peroxide.

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, 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$_2$O$_2$] and basic pH around 11, where $k_2$[H$_2$O$_2$] $\gg$ $k_0$[S] usually applies and $k_{-1}$ can be assumed to be negligible. Under these conditions, eqn (2) simplifies to $v = k_{II}[S][Fe]_{t}$. Correspondingly, the initial rate is (i) independent of [H$_2$O$_2$] in the range of (0.35–1.40) $\times$ 10$^{-2}$ M, (ii) proportional to the initial concentration of catalyst, [2], in the range of (0.375–1.50) $\times$ 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 $k_{-1}$ $\approx$ 0) and the value of the thus calculated $k_{II}$ appears in Table 1.

We have developed a mathematical tool for modelling TAML catalysis which we have used to examine the comparative behaviour of 15 different catalysts in the oxidation of one substrate under one set of conditions and, more recently, the oxidation of 5 different substrates by 2 different catalysts and 2 different oxidants at two different pHs. We used the $k_{II}$ value for 2/H$_2$O$_2$ oxidation of 1a and the $k_I$ value of (7.7 $\pm$ 0.3) $\times$ 10$^{-5}$ s$^{-1}$ determined in 2/H$_2$O$_2$ oxidation of the azo dye Orange II at pH 11 and 25 °C, 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.

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-
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 pKa of 1a (10.37 ± 0.07) indicates that the doubly deprotonated A" form dominates the speciation of 1 at pH 11, and the kH, 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 oxidation likely involves rate-limiting electron-transfer from A" 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). Intermediates of 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 enated by a monoxygenase enzyme. Intermediate 8 can undergo heterolysis to give p-hydroquinone and the compound represented by resonance structures 9 and 10 where the aromaticization provides an important component of the driving force (step iv). The absence of p-hydroquinone in the 1H NMR spectra of the crude products of the alkylation of p-hydroxy-acetophenone with methylmagnesium bromide showed the presence of which was further confirmed by ESI-MS. However, difficulties were encountered in the isolation of 11, as has been reported. As a result, we tentatively propose the intermediate to be 4-(2-hydroxypropen-2-yl)phenolate (Scheme 3, 11), the 1a analogue of a product observed in 1d oxidation by H2O2 catalysed by 2 immobilized in a layered double hydroxide composite. 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/H2O2 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 2008.

**Scheme 3** Tentative mechanism for 2/H2O2 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).

[Diagram of Scheme 3 and Scheme 4]
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.¹⁷⁴,³⁶⁶–³⁷² 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 1α 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 (Fn) versus unexposed controls (BO–Br).⁷⁷,⁹⁶,³⁸⁰–³⁸² One such study followed the effects of zebrafish exposure to 0.228 μg L⁻¹ 1α 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 1α exposure, the F1 generation was incubated for 150 days in water to which 1α was not added, highlighting that these effects may be reduced through reduction of 1α 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 1α 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 1α 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 panel¹⁴₃ and the US Food and Drug Administration⁷⁹ 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 1α at levels currently observed in the human population (earlier mini-review). However, further studies accounting for contributions to human 1α 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 1α 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 studies³⁸⁴–³⁸⁸ on the effects of human 1α exposure not discussed herein are available.⁶⁸,³⁸⁹

Exposure to 1α 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 1α during neutrophilic differentiation induced by 1.25% dimethylsulfoxide and 25 ng mL⁻¹ granulocyte-stimulating factor results in significant increases in PU.1 transcription factor activity and production of ersonal zymosan (OZ) receptor subunit CD18 and O₂⁻ 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 O₂⁻ production suggesting that long-term 1α exposure may significantly affect human immunity.³⁹⁰

Exposure of day 7 human prostaspheres, prostate stem-progenitor cells, to 1α 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 1α 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 1α dosages giving free 1α 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.³⁹³ If, to model continuous exposure throughout development, prostaspheres were exposed to 1α in vitro prior to in vivo exposure, incidences of malignant lesions further increased to 45%. These results indicate that exposure of
Critical Review

Green Chemistry

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 KATP channels as effectively as exposure to 8 nM 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 affect 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 Ca2+ results in rapid Ca2+ influxes in all three cell types leading to increases in intracellular calcium concentrations ([Ca2+]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 E221 or 1 pM 1a20 results in rapid and reversible influx of extracellular Ca2+ leading to nearly equal increases in [Ca2+]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 E221 or 1 pM 1a20 does not alter the [Ca2+]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 synergizes397 with BPA396 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 diethylstilbestrol (DES, Fig. 1),17 prenatal exposure to which is known to increase the risk of breast12 and vaginal399 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 environmental103,404 and human health405 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 development415 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 prostate91,392,416 and mammary glands417,418 to the development of cancer.105,120 Since cytochrome p450 (CYP) operates in the liver fraction S9 metabolism that gives MBP17,18 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/H2O2 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 H2O2 in the presence of 2 were less toxic than those treated with H2O2 alone. An EC50 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 H2O2 were necessary to effect this reduction in toxicity. At pH 12, the H2O2 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.

To further test for aquatic toxicity of 2/H2O2 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/H2O2 (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/H2O2 (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.

Table 2 Acute toxicity (Microtox test) of 1a, 1a + H2O2, and 1a + H2O2 + 2-treated samples. Conditions: 5 × 10−3 M 1a, 5 × 10−6 M 2, pH 12

| Reaction pH | H2O2 (equiv.) | EC50 (no 2)/% | EC50 (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               |

Fig. 7 (a) Kinetic traces of 2 (concentrations shown) catalysed oxidation of 1a (43.8 µM) by H2O2 (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).
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 including the TiPED, the mechanisms of the low dose adverse effects, the design approaches to attaining new and replacement chemicals free of such effects, 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 greening, 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 1H 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.
Green Chemistry Critical Review

W. Völkel, T. Colnot, G. A. Csanády, J. G. Filser and N. N. Bulayeva, B. Gametchu and C. S. Watson, G. S. Prins, L. Huang, L. Birch and Y. Pu, J. B. Matthews, K. Twomey and T. R. Zacharewski, W. V. Welshons, S. C. Nagel and F. S. vom Saal, J. J. Pritchett, R. K. Kuester and I. G. Sipes, E. C. Dodds and W. Lawson, S. C. Nagel, F. S. Vom Saal, K. A. Thayer, M. G. Dhar, D. E. Walsh, P. Dockery and C. M. Doolan, N. N. Bulayeva, A. Wozniak, L. L. Lash and C. S. Watson, A. L. Wozniak, N. N. Bulayeva and C. S. Watson, H. Yamada, I. Furuta, E. H. Kato, S. Kataoka, Y. Usuki, R. T. Zoeller and S. M. Belcher, J. A. McLachlan, A. Nadal, C. Sonnenschein, C. S. Watson, R. T. Zoeller and S. M. Belcher, Reprod. Toxicol., 2007, 24, 178–198.

S. Flint, T. Markle, S. Thompson and E. Wallace, J. Environ. Manage., 2012, 104, 19–34.

D. E. Walsh, P. Dockery and C. M. Doolan, Mol. Cell. Endocrinol., 2005, 230, 23–30.

E. C. Dodds and W. Lawson, Nature, 1936, 137, 996.

N. N. Bulayeva, B. Gametchu and C. S. Watson, Steroids, 2004, 69, 181–192.

G. Delbès, C. Levacher and R. Habert, Reproduction, 2006, 132, 527–538.

G. S. Prins, L. Huang, L. Birch and Y. Pu, Ann. N. Y. Acad. Sci., 2006, 1089, 1–13.

J. Cross, Z. Werb and S. Fisher, Science, 1994, 266, 1508–1518.

View Article Online

This journal is © The Royal Society of Chemistry 2017

Green Chem., 2017, 19, 4234–4262 | 4253
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. Margiinani, P. L. Palanza, L. G. Everett and R. Ragazine, 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. Domeno 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. Lauffer, 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. Urbania, G. L. Sfasciotti, O. Brugnoletti, M. Bossii and A. Polimeni, Ann. Stomatol., 2010, 1, 14–21.
81 L. N. Vandenberg, I. Chahoud, J. J. Heindel, V. Padmanabhan, F. J. R. Paumagarten 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-Register, 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. Brandebour, Mol. Cell. Endocrinol., 2009, 304, 49–54.
84 S. S. Chang, Rev. Urol., 2007, 9, S13–S18.
85 K. Čwik-Ludwicka, Rozc. 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. Margiianani, 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. Poulin, 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. Solmsen, 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. Fytii 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-Cegiło, A. R. Reindl, A. Sokolowski, 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, A. R. 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. Vandenbergh, D. R. Walser-Kuntz, C. S. Watson, W. V. Welschons, 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. Kuklenyk, 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.
Green Chemistry

This journal is © The Royal Society of Chemistry 2017

Green Chem., 2017, 19, 4234–4262 | 4257

Open Access Article. Published on 02 August 2017. Downloaded on 9/28/2021 10:02:25 PM.
This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.
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. Hönne and W. Püttmann, Environ. Sci. Pollut. Res., 2008, 15, 405–416.

235 V. G. Samaras, A. S. Stasinakis, D. Maimais, 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. Asses., 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. Mecalf, 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. M. 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., 2003, 36, 1429–1438.

246 C. A. Kinney, E. T. Furlong, D. W. Kolpin, M. R. Burhardt, 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. Eljaratt, 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. Hermesen, 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. Loub, 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. Klotserman, 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.
This journal is © The Royal Society of Chemistry 2017

Critical Review

Green Chemistry

TAML® Catalytic Oxidant Activators in the Pulp and Paper

D. A. Mitchell, A. D. Ryabov, S. Kundu, A. Chanda and N. Chahbane, D.-L. Popescu, D. A. Mitchell, A. Chanda, L. L. Tang, M. A. DeNardo, C. J. Schuler, M. R. Mills, L. L. Tang, M. A. DeNardo, C. Gayathri, R. R. Gil, R. Kanda and T. J. Collins, J. Am. Chem. Soc., 2016, 138, 2933–2936.

FAMLI® 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. Fattahaleh, Y. Hungun, 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.

N. W. Shappell, M. A. Vrabel, P. J. Madsen, G. Harrington, L. O. Billey, H. Hakki, 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.

J. L. Chen, S. Ravindran, S. Swift, L. J. Wright and N. Singhal, Water Res., 2012, 46, 6309–6318.

A. D. Ryabov, Adv. Inorg. Chem., 2013, 65, 118–163.

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.

N. R. Campbell, Proc. R. Soc. London, Ser. B, 1940, 129, 528–538.

E. E. Reid and E. Wilson, J. Am. Chem. Soc., 1944, 66, 967–969.

T. Hirano, Y. Honda, T. Watanabe and M. Kuwahara, Biosci. Biotechnol. Biochem., 2000, 64, 1958–1962.

T. T. Schug, R. Abagan, 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. Patiasul, T. L. Tal, K. A. Thayer, L. N. Vandenbergen, 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.

P. George, Biochem. J., 1953, 55, 220–230.

H. A. Balsiger, R. de la Torre, W.-Y. Lee and M. B. Cox, Sci. Total Environ., 2010, 408, 1422–1429.

E. J. Routledge and J. P. Sumpter, Environ. Toxicol. Chem., 1996, 15, 241–248.

L. Truong, D. M. Reif, L. St. Mary, M. C. Geier, H. D. Truong and R. L. Tanguay, Toxicol. Sci., 2014, 137, 212–233.

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.

M. A. Mendez, M. F. Suarez and M. T. Cortes, J. Electroanal. Chem., 2006, 590, 181–189.

I. L. Kogan and K. Yakushi, Electrochim. Acta, 1998, 43, 2053–2060.

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.

M. Emelianenko, D. Torrejon, M. DeNardo, A. Socolofsky, A. Ryabov and T. Collins, J. Math. Chem., 2014, 52, 1460–1476.

M. A. DeNardo, Ph.D. Dissertation, Carnegie Mellon, March 26, 2016.

J. S. Dordick, M. A. Marletta and A. M. Klibanov, Biotechnol. Bioeng., 1987, 30, 31–36.

M. Reihmann and H. Ritter, Adv. Polym. Sci., 2006, 194, 1–49.

S. Kobayashi, H. Kurioka and H. Uyama, Macromol. Rapid Commun., 1996, 17, 503–508.

H. Sakuyama, Y. Endo, K. Fujimoto and Y. Hatano, J. Biosci. Bioeng., 2003, 96, 227–231.

S. Kobayashi, H. Uyama, T. Uchiyama and H. Kurioka, Macromol. Chem. Phys., 1998, 199, 777–782.

H. Uyama, N. Maruichi, H. Tonami and S. Kobayashi, Biomacromolecules, 2002, 3, 187–193.

J. Kulyš, R. Vidziunaitė, A. Ziemys and I. Bratkovskaja, Biologiija, 2007, 53, 40–44.

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.

S. Arulmozhiraja, M. L. Coote, Y. Kitahara, M. Juhász and T. Fujii, J. Phys. Chem. A, 2011, 115, 4874–4881.

B. Kolvenbach, N. Schlaich, Z. Raoui, J. Prell, S. Zühlke, T. Fukuda, H. Uchida, Y. Takashima, T. Uwajima, T. Sugihara and H. Kurioka, J. Phys. Chem. A, 2011, 115, 4874–4881.

This journal is © The Royal Society of Chemistry 2017

Green Chemistry

View Article Online

This article is licensed under a Creative Commons Attribution 3.0 Unported Licence.
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 J. Matsumoto, H. Yokota and A. Yuasa, *Environ. Health Perspect.*, 2002, 110, 193–196.

410 C. P. Strassburg, A. Strassburg, S. Kneip, A. Barut, R. H. Tukey, B. Rodeck and M. P. Manns, *Gut*, 2002, 50, 259–265.

411 J. Matsumoto, H. Yokota and A. Yuasa, *Environ. Health Perspect.*, 2002, 110, 193–196.

412 S. M. Engel, B. Levy, Z. Liu, D. Kaplan and M. S. Wolff, *Reprod. Toxicol.*, 2006, 21, 110–112.

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. Rikihiwa 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.