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1 **Learning from the past and considering the future of chemicals in the**
2 **environment**

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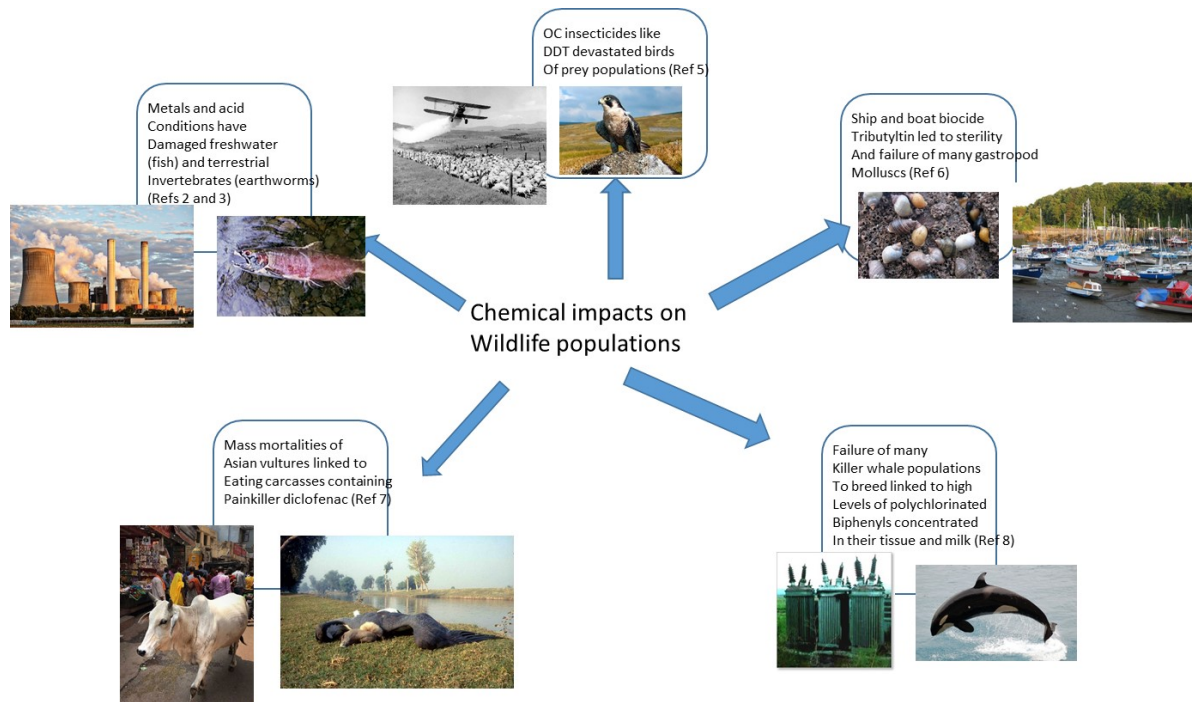
15 **ABSTRACT**

16 Knowledge of the hazards and associated risks from chemicals we discharge to the
17 environment has grown considerably over the past 40 years. This improving situation stems
18 from advances in our ability to measure chemicals at low environmental concentrations,
19 recognition of a range of effects on organisms, and a worldwide growth in expertise.
20 Environmental scientists and companies have learnt from the experiences of the past and in
21 theory the next generation of chemicals will cause less acute toxicity, be less persistent and
22 bioaccumulative. However, we still struggle to establish if the non-lethal effects associated
23 with some modern chemicals and substances will have serious consequences for wildlife. It
24 remains a challenge to obtain the resources appropriate to the magnitude of chemical
25 challenges that lie ahead.

26 **Past and present examples**

27 Synthetic chemicals have provided dramatic improvements in food production and living
28 standards (*1*). Although there are concerns over many hundreds of chemicals in the
29 environment, there are only a few, albeit very important, examples of chemicals actually
30 harming wildlife populations (Fig. 1). These examples showed us that hydrophobic
31 (lipophilic) chemicals could both persist in the environment but also bioconcentrate, meaning
32 the highest exposures would manifest themselves in long-lived top-predators. We also learnt
33 that tests of acute toxicity on a necessarily limited range of laboratory-friendly species were

34 not predictive for all species and effects so that more chronic tests on a wider range of
 35 organisms were needed. Knowledge gained from such disasters should make the use of
 36 chemicals increasingly safer. However, our past failures suggest we must be prepared for
 37 more surprises in future.



38

39 Figure 1. Classic examples of where chemicals actually have had or are having population
 40 level effects (2-6) (7) (8)

41

42 **The proportion of chemicals for which we have adequate environmental information**

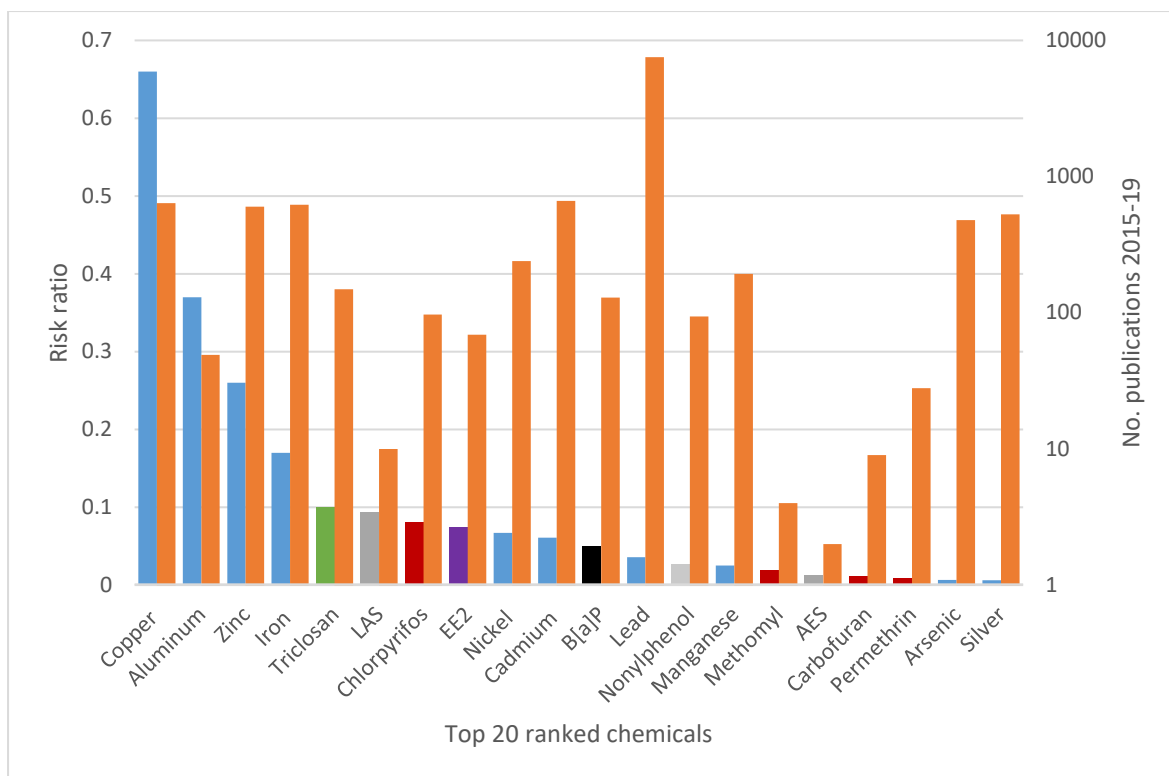
43 The number of chemicals and substances on the market in places like the US and Europe,
 44 where data are accessible, is believed to be in the region of 75,000 to 140,000 (9, 10). Yet it
 45 is estimated we only have empirical data on persistence available for 0.2%, bioconcentration
 46 data for 1% and aquatic toxicity for 11% of chemicals registered in the EU (11, 12) and
 47 there is a similar message from the US (9). In the absence of such hard information for the
 48 majority of chemicals, some help on the risks we face can come from computational
 49 predictive methods (9, 11). Nevertheless, the task is complicated by the formation of
 50 breakdown products in the environment for which we have less or no information. An
 51 additional challenge to our efforts to assess risk from these many chemicals entering the

52 environment is the potential for mixture effects. This may lead to higher impacts on
53 organisms than would have been predicted on the basis of individual chemical based risk
54 assessments (13). Today's research funding model tends to encourage widening and
55 deepening studies on the current chemical, or group of chemicals, perceived to be of most
56 concern, rather than supporting research on a higher proportion of the chemicals being
57 discharged and considered potentially problematic (14).

58 **Chemical risks are not equal and nor is exposure**

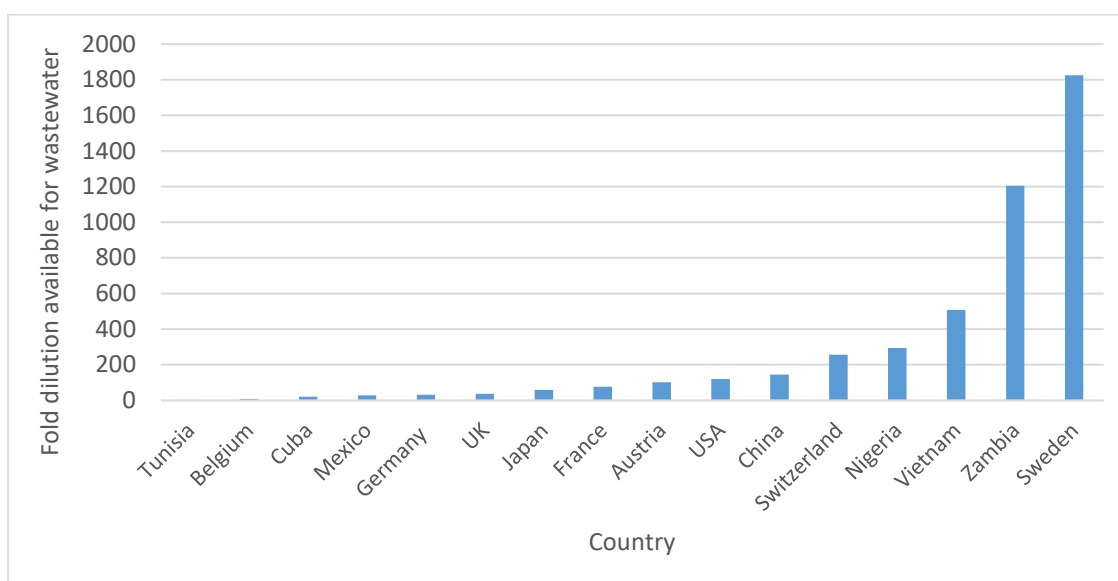
59 Given the vast array of chemicals contaminating our natural environment, which are
60 deserving of our greatest attention? For example, the risk of copper harming wildlife is
61 reported to be 5-orders of magnitude higher than the drug atenolol (15) when comparing
62 median exposure with median toxicity values for rivers in the United Kingdom. In other
63 words, atenolol represented only 0.001% of the copper problem. In fact, metals dominated
64 the top ten of 71 chemicals of concern studied in the United Kingdom (15) (Fig. 2) and are
65 similarly highly ranked in China (16).

66 Chemical exposure from wastewater is not evenly spread around the world. This can be
67 expressed as the extent to which the wastewater generated by an individual will be diluted by
68 the natural river flow (17). Depending on landmass, population size and rainfall, some
69 countries will face constant and widespread elevated exposure to chemicals in wastewater
70 and others much less so (Fig. 3).



71

72 Figure 2 – The highest ranked 20 chemicals from a pool of 71 common chemicals found in
 73 British Rivers ranked on the basis of the ratio of median river concentration vs the 5th
 74 percentile of aquatic ecotoxicity data. Data from Johnson et al 2017 (15). Also shown, as
 75 orange bars, are the number of publications found on Web of Science in September 2019
 76 under the search chemical AND environment AND risk for the period 2015-2019 for the
 77 same chemicals. Note LAS is linear alkylbenzene sulfonates, EE2 is ethinylestradiol, B[a]P
 78 is benzo[a]pyrene and AES is alcohol ethoxysulfates.



79

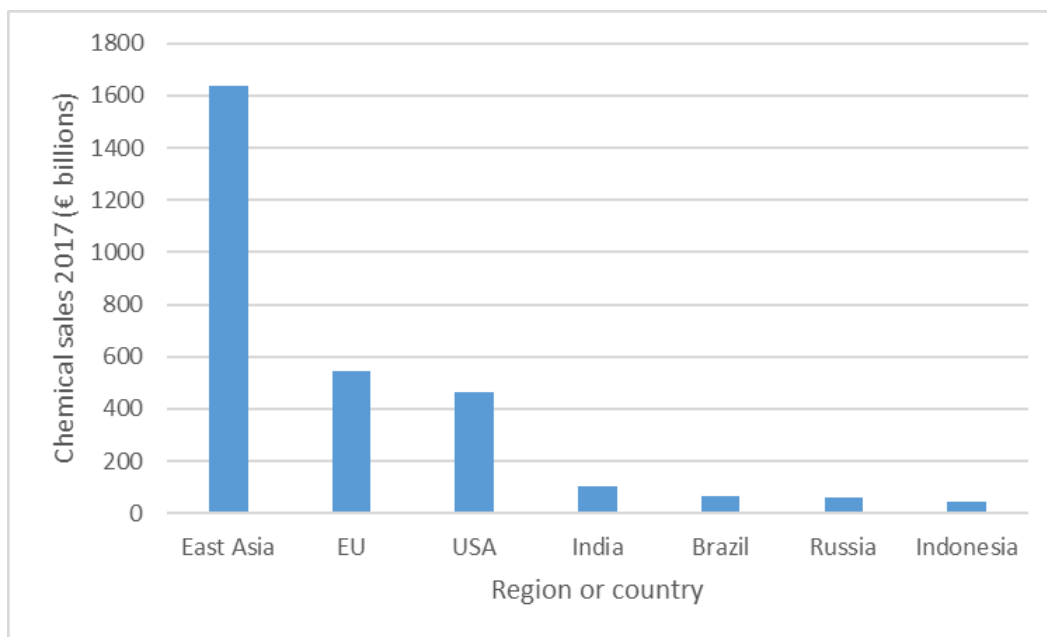
80 Figure 3. A few examples of the relative dilution of an individual's wastewater based on the
81 median annual natural flow in their rivers for different countries. Data from (17)

82 **New chemicals and new places of concern**

83 There is an extraordinary diversity of services that modern society expects chemicals to
84 supply. Examples include medicines, flame retardants and pesticides. We now recognise
85 that the very properties that can make them work well for us can at the same time be
86 deleterious for the wider environment. As medical knowledge grows, the expectation for
87 new pharmaceutical-based treatments for diverse health conditions will continue. A current
88 example is the clear incentive for drug companies to devise more effective compounds to
89 treat a range of age-related conditions (18). Ethinylestradiol has been a very effective oral-
90 contraceptive, but the combination of its potency and persistence made it an important
91 contributor to endocrine disruption in wild fish downstream of wastewater effluent (19). We
92 now know that if some of the new pharmaceuticals act as agonists or antagonists on the
93 endocrine system, then the estrogen-based disruption story might be repeated with our fellow
94 vertebrate, the fish (20). Following problems with the persistence and toxicity of
95 polybrominated diphenyl ethers, the range of replacement candidate flame retardants are now
96 much wider, including non-halogenated organic or metal compounds with phosphate groups,
97 hydroxide or stannate groups (21). Concerns over pesticide mobility, non-target toxicity and
98 persistence have drastically reduced the number of products for sale. The approaches of
99 tomorrow are likely to be more precisely pest-targeted including RNA interference,
100 pheromones and sterility. These new flame retardants and insecticides should be much safer,
101 but we must be alert to surprises. Neonicotinoid use (an insect-specific post-synaptic agonist)
102 had been considered sustainable, but now it is not (22).

103 The modern economy has been transformed by globalization. For chemicals this has meant
104 the transfer of much chemical production to Asia (23), where chemical sales are 168% of the
105 US and Europe combined (Fig. 4). However, in some cases weak regulation or uneven local
106 enforcement has led to examples of severe pollution hotspots. Examples include atmospheric
107 contamination with chlorofluorocarbons (CFCs) coming from the Shandong and Hebei
108 provinces of China (24), gross perfluorooctanoic acid (PFOA) pollution from a vast Chinese
109 manufacturing site (25) and antibiotics from a manufacturing plant in India (26). However, it
110 must be recognised that successful management of industrial waste and indeed pollution is far
111 from straightforward. It is one thing to set water quality targets, but these can only work

112 where there is a clearly independent regulator taking consistent high quality measurements
113 with an independent judiciary to apply to, both supported by local and national governments.
114 The degree to which environmental protection is improved by centralisation or when it is
115 devolved to local administrations is debatable (27). In the case of local governance in China,
116 there is evidence for uneven application of regulations (28, 29). Protection is also boosted by
117 a national commitment to transparency, in which the scrutiny by the public, environmental
118 non-governmental organisations and journalists are accepted. This is not a given throughout
119 the world (30, 31).



120

121 Figure 4. The level of chemical sales in 2017. East Asia includes China, Japan and South
122 Korea (23)

123 **Reasons for optimism**

124 **1. Progress in regulation and management of chemicals in the environment**

125 Chemical regulations in the 1960s and 70s concentrated on remediating past pollution and
126 controlling the emission of a limited number of pollutants. This became forward-looking so
127 that new chemicals wishing to enter the market should conform to minimum human safety
128 and environmental standards. Examples would be the “Toxic Substances Control Act”
129 (TSCA) in 1976 (Public Law 94-469) in the US and Registration, Evaluation, Authorisation
130 and Restriction of Chemicals (REACH) (EC 1907/2006) in the EU. Given the many chemicals

131 that entered the market before these laws were enacted, a retrospective authorization process
132 is trying to catch up. Whilst not perfect, the establishment of regulations like TSCA and
133 REACH set an important precedent that the onus to demonstrate a chemical was safe for
134 humans and the environment should lie with the manufacturer. The phrase in Europe is ‘no
135 data, no market’ (32).

136 **2. Analytical developments, knowledge of undesirable chemical characteristics and** 137 **alternatives to animal testing**

138 Developments in analytical chemistry continue to drive down limits of detection. The
139 opportunity is now also arising to search for and tentatively identify all the molecules present,
140 known and unknown, with non-targeted screening methods (NTS) (33). Recent examples
141 where NTS has opened a window include revealing the range of compounds found in urban
142 runoff (34), to being able to fingerprint unusual pollution incidents and to identify the
143 industrial premises responsible (35). A recent intriguing development is acquiring historic
144 analytical raw data from previous studies for the retrospective analysis for “new” pollutants
145 that were not originally targeted (36). These new approaches will help to make the
146 environment more transparent with respect to chemical contaminants.

147 There is now much shared knowledge on the undesirability of properties such as
148 hydrophobicity and persistence in chemicals that we intend to discharge to the environment. In
149 the consumer goods industry, recognition of poor biodegradability has now led to replacement
150 of branched alkylbenzene sulphates by linear forms, the replacement of long chain dialkyl
151 quaternary surfactants by ester-based quaternaries, nonylphenol ethoxylates (also having toxic
152 concerns) by alcohol ethoxylates, and the replacement of musk xylene by macrocyclic musks.
153 Although not driven primarily by environmental concerns, an increasing proportion of new
154 pharmaceuticals being registered are the so-called biologics. For example, 12 of the 30 new
155 drugs registered for the German Market in 2016 noted by the German Pharma Association, and
156 75 of the recent top 200 selling retail drugs in the USA (37), are made from biological material
157 such as proteins, genes, allergens and cells, which are considered not to pose the persistence
158 issues of small synthetic molecules.

159 There is an understandable reluctance to submit the vast numbers of animals needed for
160 laboratory toxicity tests for the many thousands’ of chemicals that still need to be registered,
161 and this has stimulated toxicity and exposure model developments (9). Computer models have

162 been used to help predict which chemicals are going to be of greatest concern (in silico risk
163 assessment); in other words those that will be persistent, bioaccumulative and toxic (PBT). In
164 a survey of 95,000 chemicals, the model predicted that only 3 to 5% were likely to be PBT
165 (11).

166 **3. Better wastewater treatment and International chemical initiatives**

167 There are considerable benefits, not just to general water quality, but to chemicals reduction
168 by moving from primary wastewater treatment (settling) to secondary treatment (biological)
169 and increasing the biological treatment time in secondary treatment from simple methods like
170 trickling filters to activated sludge (38, 39). The widespread adoption of the activated sludge
171 process (ASP) in towns and cities around the world, with its biological treatment time of 8 h
172 or more, has done a great deal to protect rivers from the worst consequences of high chemical
173 exposures. In China, it is now reported that 94% of the urban population have wastewater
174 treatment with 81% using advanced processes like ASP (40). Whilst not perfect, their
175 introduction can significantly improve water quality and hence biodiversity when compared
176 to more historic and less efficient treatment (38). It is within our power, if we wish it, to
177 introduce stringent tertiary treatment, to eliminate all organics from effluent, and this is being
178 applied in some parts of Switzerland (41)

179 Developed and many developing countries share many of the same chemical challenges and
180 this is particularly true for many persistent pollutants which know no boundaries. Thus, it is
181 encouraging to see international agreements on POPs (Stockholm Convention), mercury
182 (Minamata Convention) hazardous waste disposal (Basel Convention), and certain hazardous
183 chemicals and pesticides (Rotterdam Convention). Sensible advice on managing chemicals
184 including legal, economic, technical and voluntary instruments including the adoption of safer
185 alternatives is now available to all countries (42).

186 **Reasons for pessimism**

187 **1. Continuing uncertainty over the importance of non-lethal effects**

188 Once we move away from apical end-points (non-lethal or end-points which disrupt
189 reproduction or growth), it remains a matter of speculation as to whether the response to a
190 chemical seen in the laboratory really translates to harm to individuals or populations in the

191 wild. The detailed mechanistic detection work of an adverse outcome pathway (AOP), in
192 theory, predicts the harmful outcome of effects from the molecular level all the way up to that
193 of the population (43). AOPs have confidently predicted population effects on fish from
194 endocrine disruptors (44), and yet this has not been observed in the field (45). It is presently
195 unclear if the development of AOPs will aid in the environmental risk assessment of
196 chemicals. Can gene, protein or metabolite expression studies on their own, be predictive of
197 actual impacts on wildlife populations or indeed food webs (46)?

198 **2. Data quality and the relevance of research topics**

199 It is now widely accepted that a significant proportion of published research is not
200 reproducible, a situation sometimes called the ‘reproducibility crisis’ (47, 48) (49). Reasons
201 include: perverse incentives on research scientists to publish ‘exciting’ research and a general
202 lack of training of researchers (50). Two common problems are poor experimental design and
203 bias (51). In ecotoxicology, many scientists conduct their research on animals not routinely
204 used in regulatory tests, and which other researchers rarely utilise.

205 The focus of public concern over chemicals is unpredictable. This can lead to sudden
206 demands for information which can overwhelm everything else. Inevitably, many fundable
207 topics will have to be dropped in order to concentrate on an area of new concern. A dramatic
208 growth area has been nanoparticles and the environment, which when searched under Web of
209 Science reveals interest has grown from 36 papers/yr in 2000 to 4,200/yr in 2017. Yet many
210 studies appear to show a modest relative risk, at least for common metal-based nanoparticles
211 (15, 52). Another example might be bisphenol-A, an additive used in many plastic items,
212 which has been shown to be a weak estrogen. Many hundreds of studies have been published
213 on its presence and possible harm to the environment (WoSTM finds 630 papers when BPA,
214 effect and environment are the search terms in September 2019). Yet the evidence that
215 bisphenol-A is adversely affecting wildlife is essentially non-existent (53). On the other hand,
216 we have many thyroid active, cardiovascular, antiepileptics and muscle relaxant drugs for
217 which few if any studies have been carried out on their possible effects on aquatic wildlife.

218 It might surprise many people to learn that often the focus of research into chemicals in the
219 environment is not necessarily linked to their relative risk. For the top 20 highest risk ranked
220 chemicals in British rivers (Fig. 2) we found that publications related to their environmental

221 risk varied between 7,531 for lead to only 2 for the anionic surfactant, alcohol ethoxysulfates
222 in the period 2015-2019 (Fig. 2).

223 This area of science is prone to the ‘bandwagon’ effect, by which many papers only
224 demonstrate what we knew already: did we need 250+ papers to tell us that ethinylestradiol
225 poses a risk to fish? Everything we needed to know to protect the environment we knew from
226 the first half a dozen papers. A current trend is this desire to search for more-and-more subtle
227 ‘effects’, such as one or a few genes being tweaked a tad, when the consequences of those
228 effects are completely unknown.

229 **3. Risk assessments are getting further behind and scientists tend to stay in their**
230 **silos**

231 Thorough risk assessment is costly and can require decades of research. Given the range of
232 species and number of end-points that could be examined, it seems certain we will never
233 catch up using our traditional approaches (54). If this assertion is correct, then persevering
234 with the present testing strategy does not seem appropriate. Ethical objections to the use of
235 animals, particularly vertebrates, in tests are increasing, yet we continue to add more tests to
236 the Organisation of Economic Cooperation and Development (OECD) battery of accepted
237 (eco) toxicity tests. Re-thinking how the environmental risks of a chemical can be assessed,
238 with a bigger role for predictive modelling of harmful properties, is ongoing, but regulators
239 remain cautious about placing reliance on such information (55)

240 The study of chemicals in the environment appears to revolve largely around the two
241 disciplines of ecotoxicology and environmental chemistry. It is common for ecotoxicologists
242 in their publications to state that ‘effects were observed at environmentally relevant
243 concentrations’ whilst environmental chemists for their part are often tempted to assert that
244 their ‘highest measured concentrations exceeded reported effect (toxic) concentrations’ (56).
245 Such statements imply there are problems out there, possibly very big ones. However, it is
246 unclear, based on the evidence of ecotoxicology and environmental chemistry alone, whether
247 we are exaggerating the dangers and so over-regulating or alternatively underestimating risks
248 (such as been proposed from mixture effects) and so failing to protect (54). There is a 3rd
249 community of scientists, who in theory have much to offer in assessing chemical impacts on
250 wildlife and these are ecologists. The presence of long-term wildlife, monitoring is vital for
251 such research. But we still see surprisingly few examples of collaboration between

252 ecologists, ecotoxicologists and environmental chemists. Ecologists have highlighted
253 alarming declines in some wildlife(57, 58), and despite many confounding variables, long-
254 term ecological data can be extremely compelling at establishing a link that can cut across
255 competing arguments, such as with neonicotinoids and bees (22, 46). To determine the true
256 harm of chemicals, these different scientists will need to collaborate closely (59).

257 **Conclusions**

258 Adapting to the immensely difficult societal and environmental challenges of tomorrow will
259 undoubtedly require new chemicals and chemical solutions. The production of chemicals,
260 their diversity and use around the world has never been greater. Our ability to manage the
261 risks are finely balanced, with reasons to be both pessimistic and optimistic. Unfortunately,
262 the sheer number of chemicals on the market, and presumably also entering the environment,
263 are currently beyond our ability to assess the risks from them all. Although there are no
264 guarantees, our past knowledge married to ‘in silico’ modelling of hazards are helpful in
265 gauging relative risk. Provided we maintain long-term wildlife monitoring efforts,
266 particularly in areas of land or water most exposed to chemicals, we may have some
267 confidence that our use of chemicals is sustainable.

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340

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