

1 **Estimating Burden and Disease Costs of Exposure to Endocrine Disrupting Chemicals in**
2 **the European Union**

3

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38 Recommendations Assessment, Development and Evaluation (GRADE); polybrominated
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56 **Abstract**

57 **Context:** Rapidly increasing evidence has documented that endocrine disrupting chemicals
58 (EDCs) contribute substantially to disease and disability.

59 **Objective:** To quantify a range of health and economic costs that can be reasonably attributed to
60 EDC exposures in the European Union.

61 **Design:** A Steering Committee of scientists adapted the Intergovernmental Panel on Climate
62 Change weight-of-evidence characterization for probability of causation based upon levels of
63 available epidemiologic and toxicologic evidence for one or more chemicals contributing to
64 disease by an endocrine disruptor mechanism. To evaluate the epidemiologic evidence, the
65 Steering Committee adapted the WHO Grading of Recommendations Assessment, Development
66 and Evaluation (GRADE) Working Group criteria, while the Steering Committee adapted
67 definitions recently promulgated by the Danish Environmental Protection Agency for evaluating
68 laboratory and animal evidence of endocrine disruption. Expert panels used the Delphi method
69 to make decisions on the strength of the data.

70 **Results:** Expert panels achieved consensus for probable (>20%) EDC causation for IQ loss and
71 associated intellectual disability; autism; attention deficit hyperactivity disorder; childhood
72 obesity; adult obesity; adult diabetes; cryptorchidism; male infertility and mortality associated
73 with reduced testosterone. Accounting for probability of causation, and using the midpoint of
74 each range for probability of causation, Monte Carlo simulations produced a median cost of €157
75 billion (1.23% of EU Gross Domestic Product) annually across 1000 simulations. Notably, using
76 the lowest end of the probability range for each relationship in the Monte Carlo simulations
77 produced a median range of €~~119~~109 billion that differed modestly from base case probability
78 inputs.

79 Conclusions: EDC exposures in the EU are likely to contribute substantially to disease and
80 dysfunction across the life course with costs in the hundreds of billions per year. These estimates
81 represent only those EDCs with the highest probability of causation; a broader analysis would
82 have produced greater estimates of burden of disease and costs.

83 **Introduction**

84

85 The European Union defines an endocrine disrupting chemical (EDC) as an “exogenous
86 substance that causes adverse health effects in an intact organism, or its progeny, secondary to
87 changes in endocrine function” (1-3). EDCs are diverse in their chemical structure, but all known
88 EDCs interfere with hormone action to cause adverse effects, resulting in increased incidence of
89 disease/dysfunction (3). For example, the water contaminant perchlorate is an EDC because it
90 directly inhibits thyroid hormone synthesis, restricting the availability of thyroid hormone in
91 target tissues, thereby interfering with thyroid hormone action (e.g., (4)); while BPA is an EDC
92 in part because it can act through the estrogen-related receptor-gamma to alter insulin production
93 and release, thus contributing to the pathogenesis of insulin resistance and type 2 diabetes(5).

94 The past twenty years have produced a great deal of new information from experimental
95 studies focused on molecular, cellular and animal experiments (6) as well as epidemiological
96 studies demonstrating that a wide array of chemical structures –pharmaceuticals, personal care
97 products, commercial chemicals and environmental pollutants – can interfere with hormone
98 action. Among the chemicals known to be EDCs are diethylstilbestrol (DES) (7),
99 polychlorinated biphenyls (PCBs), dioxins, perfluoroalkylcompounds, solvents, phthalates(8),
100 bisphenol A (BPA)(9), dichlorodiphenyldichloroethylene (DDE)(10), organophosphate and
101 organochlorine pesticides(11), and polybrominated diphenyl ethers (PBDE)(12, 13). These
102 chemicals have been shown to interfere with a variety of endocrine pathways including estrogen
103 (14), androgen (14), thyroid(15, 16), retinol(17), aryl hydrocarbon and peroxisome proliferator-
104 activated receptor pathways(18). The chemicals are widely used in consumer products,
105 electronics and agriculture and widespread human exposures occur. Many EDCs are food

106 contaminants (e.g., pesticides, BPA and phthalates), though inhalation and dermal absorption are
107 known pathways for human exposure. Potential consequences of exposure to EDCs include
108 infertility and male and female reproductive dysfunctions(19), prostate and breast cancer(20),
109 birth defects(21), obesity(22, 23), diabetes, cardiopulmonary disease, neurobehavioral and
110 learning dysfunctions and immune dysregulation (24). Laboratory data on these associations are
111 supplemented by varying levels of epidemiologic evidence for each chemical-
112 disease/dysfunction dyad. In part due to uncertainty of causation, no estimate of the health or
113 economic burden of EDCs has been made. Systematic estimates of burden of disease attributable
114 to EDC exposures could help inform decision-making that protects public health.

115 The European Union is taking the lead on regulating EDCs, through legislation such as
116 REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) and regulations
117 on pesticides and biocides(25). The outcome of these policy discussions will be crucial not only
118 for consumer and public health protection in the EU, but will also set scientific and regulatory
119 policy precedents for other national policies including those consistent with implementation of
120 global agreements such as SAICM (the Strategic Approach to International Chemicals
121 Management)(26). A critical element of the regulation of EDCs in EU policy will be the criteria
122 by which test outcomes for EDCs are translated into regulatory action. These criteria will
123 determine, based on the functional properties of each chemical and responses measured in
124 appropriate test systems, whether it will be restricted, phased out, or allowed to enter or remain
125 on the EU market. The EU Commission has requested that an impact assessment be conducted to
126 assess the economic implications of the criteria under discussion(27). The impact assessment is
127 focused on the economic impact to industry of regulating EDCs in Europe. Our goal here is to

128 estimate the health and economic benefit of regulating EDCs in Europe, as based on current
129 evidence.

130

131 We now describe the general methods used to attribute disease and disability to EDCs, to weigh
132 the probability of causation based upon the available evidence, and to translate attributable
133 disease burden into costs. During a two-day workshop in April 2014, five expert panels
134 identified conditions where the evidence is strongest for causation, and developed ranges for
135 fractions of disease burden that can be attributed for EDCs. While accompanying manuscripts
136 describe in greater detail the bases for their estimates of disease attribution and probability of
137 causation, we present here an overview of the methods they applied as well as approaches
138 applied to estimate disease burden and costs attributable to EDCs in the EU based upon those
139 data inputs.

140

141 **Methods**

142

143 *General Approach*

144

145 In 1981, the Institute of Medicine developed a general approach to assess the "fractional
146 contribution" of the environment to causation of illness in the U.S., which remains widely used
147 to this day and is depicted in Equations 1 & 2.(28)

148

Attributable disease burden = Disease rate x AF x Population size (Equation 1)

Attributable Costs = Disease rate x AF x Population size x Cost per case (Equation 2)

149

150 where "Cost per case" refers to discounted lifetime expenditures attributable to a particular
151 disease including direct costs of health care, costs of rehabilitation, and lost productivity; Disease
152 rate and Population size refer, respectively, to either the incidence or prevalence of a disease and
153 the size of the population at risk; and AF is the Attributable Fraction, which is defined by Smith
154 et al. in the context of environmental health as "the percentage of a particular disease category
155 that would be eliminated if environmental risk factors were reduced to their lowest feasible
156 concentrations."(29) The AF is a composite value and is the product of the prevalence of a risk
157 factor multiplied by the relative risk of disease associated with that risk factor(30), and is
158 estimated using the following equation:

159

$AF = \text{Prevalence}_{\text{exposure}} * (RR-1) / [1 + (\text{Prevalence}_{\text{exposure}} * (RR-1))]$, (Equation 3)

160

161 Where RR is the relative risk of morbidity associated with the exposure. An alternative
162 formulation of Equation 1 would presuppose an exposure-outcome relationship that would result
163 in discrete calculations of the increment in disease or disability over and above a comparison,
164 unexposed group, and is presented in Equation 4:

165

Disease burden = Incremental prevalence or incidence x Population size (Equation 4)

166

167 *Accounting for Uncertainty and Probability of Causation*

168 In the past, certainty of causation, however defined, has been presumed a requirement prior to
169 pursuing estimates of attributable disease burden or costs, when in reality causation is not simply
170 binary. In his widely cited work about the criteria for causation, Sir Austin Bradford Hill
171 acknowledged the reality that “[a]ll scientific work is incomplete – where it be observational or
172 experimental,” noting that uncertainty “does not confer upon us a freedom to ignore the
173 knowledge we already have, or to postpone the action that it appears to demand at a given
174 time.”(31) The Intergovernmental Panel on Climate Change (IPCC) has managed uncertainty by
175 applying a weight-of-evidence characterization for probability of causation.(32) A steering
176 committee of scientists overseeing the project (MB, JD, PG, JH, AK, PM, LT, RZ) adapted the
177 IPCC approach to assessing probability of causation based upon the available epidemiologic and
178 toxicologic evidence for one or a group of chemicals contributing to disease by an endocrine
179 disruptor mechanism. The schema is presented in Table 1, and subsequent paragraphs delineate
180 the approach to evaluating epidemiologic and toxicologic evidence.

181

182 To evaluate the epidemiologic evidence, the GRADE Working Group criteria(33, 34) were
183 adapted as they were recently applied in evaluating indoor air quality criteria by the World
184 Health Organization(35). As described in Table 2, the criteria utilize study designs as a primary
185 basis for distinguishing strength of evidence, with factors specific to the studies (both

186 individually and in the aggregate) such as potential bias, limitations, strength of dose-response
187 relationships, residual confounding, consistency and analogy permitting upward and downward
188 grading of the quality of evidence.

189
190 To evaluate the toxicologic evidence, the steering committee adapted criteria recently
191 promulgated by the Danish Environmental Protection Agency for evaluating laboratory and
192 animal evidence of endocrine disruption(36). The schema is presented in Table 3. Identification
193 of an endocrine mechanism/mode of action and corroboration of toxicity in laboratory model
194 studies was required to assess the toxicological evidence for the exposure-outcome association as
195 Group 1 (Endocrine disruptor). Group 2A (Suspected endocrine disruptor) required either (1) the
196 presence of endocrine disruptor mode of action without clear corroboration of the mode of action
197 producing the expected adverse effects in laboratory or animal studies, or (2) the presence of the
198 adverse effects in laboratory animal studies with a suspected endocrine mode of action.
199 Exposure-outcome associations were evaluated to have group 2B (Potential endocrine disruptor)
200 toxicological evidence when there was evidence of adverse effects in animal studies that could
201 have either endocrine mode of action or a non-endocrine mode of action or in vitro/in silico
202 evidence indicating a potential for endocrine disruption in intact organisms.

203

204 *Quantifying Attributable Burden*

205

206 The steering committee noted three general approaches on which to base attribution to EDCs: (1)
207 trends in incidence/prevalence over and above a baseline that would be difficult to attribute to
208 genetics accompanied by information on likely causal mechanisms by EDCs and/or increasing

209 exposure, (2) data from genetic studies that permit quantification of the remaining environmental
210 contribution (within which one might posit EDC to contribute a portion), and (3) dose-response
211 relationships from the epidemiologic literature. In general, the steering committee prioritized the
212 third approach. In the absence of epidemiologic evidence for a dose-response relationship, the
213 presence of toxicologic data documenting effect and mechanism and/or other data might suggest
214 a strong basis from which to reason an incremental effect in humans. In this scenario, the first
215 two lines of evidence would add support to an estimate of the degree that one or more EDCs
216 might contribute to the condition under consideration.

217
218 While chemicals banned by Europe (e.g., under the Stockholm Convention) have been
219 documented to be endocrine disruptors and contribute to disease and disability, panels were
220 advised not to examine effects of these exposures unless there was a compelling case that
221 interventions outside Europe could influence disease and disability in Europe. For example, the
222 obesity panel did not quantify the obesogenic and diabetogenic effects of other EDCs that
223 continue to contaminate the EU general population (e.g., polychlorinated biphenyls and
224 hexachlorobenzene) because they are banned under the Stockholm Convention(37, 38). In
225 contrast, DDE-attributable obesity and diabetes could be prevented through further reductions in
226 DDT use globally, which is substantially relevant due to the current use of this chemical for
227 malaria control and its long-range transport and persistence in the environment (39).

228
229 Panels were advised to consider all possible developmental windows of vulnerability, but to
230 focus on exposure timing and duration with the strongest evidence for causation from
231 toxicological and epidemiologic data. When a dose-response relationship was identified for a

232 particular exposure period, this relationship was applied to the EU population based upon
233 biomarker data available from large surveys or pooled data from multiple studies in individual
234 countries. Biomarkers were then estimated for quantiles (usually 0-9th, 10-24th, 25-49th, 50-74th,
235 75-89th, 90-99th) in recognition that narrower quantiles might reduce precision of estimates. In
236 the rare circumstance that there were no epidemiologic studies on which to assess a dose-
237 response relationship, but there existed enough evidence to suggest an effect in a portion of the
238 appropriate population, a relative risk was estimated, and a prevalence of exposure was identified
239 in order to estimate an attributable fraction, using Equation 3. Whenever possible, the most
240 population-representative data were used for appropriate exposure and/or biomarker inputs, as
241 convenience samples may have unmeasurable biases resulting in misestimation of exposure, and
242 these inputs were applied consistently across all the exposure-outcome associations studied.

243

244 *Approach to Evaluating Evidence*

245

246 Following the WHO/UNEP State of the Science of Endocrine Disrupting Chemicals, which
247 identified three distinct sets of health endpoints with the most substantial evidence for EDC
248 attribution (obesity/diabetes, male reproductive health and neurodevelopmental disability) (24),
249 the steering committee convened expert panels for each of the domains composed of four to
250 eight scientific experts. Two expert panels were also convened for breast cancer and female
251 reproductive conditions; their deliberations followed an identical process to that described below,
252 are nearing completion, and will be the basis for future reports. The steering committee
253 identified epidemiologic and toxicologic experts based upon their scholarly contribution in the
254 diseases under consideration and endocrine disruptor toxicology, and invited them to attend a

255 two-day scientific meeting in Paris, which was held at the French National Alliance for Life
256 Sciences and Health from April 28-29, 2014.

257
258 During this meeting, the steering committee applied a modified Delphi approach (40) to
259 evaluating the strength of the epidemiologic and toxicological evidence, and the nature of the
260 association between exposures and outcomes. The Delphi method was developed on the premise
261 that group judgments are more valid than those of individuals. While named after the oracle at
262 the sanctuary dedicated to Apollo in the 5th century BC, the method is not mystical and was first
263 developed at the beginning of the Cold War to forecast technological impacts on warfare (41).
264 Helmer, Dalkey and Rescher at the RAND Corporation formalized the method in the 1950s for
265 science and technology forecasting(42). It has been applied successfully and with high
266 consistency and rigor across many disciplines including health and education.(43-46)

267
268 Teleconferences were held biweekly over a three-month period with participants to encourage
269 familiarity with literature being reviewed, to describe the Delphi method (including definition of
270 terminology and interaction structure),(41) and to identify group leaders (PG, RH, JL). An initial
271 presentation at the beginning of the two-day meeting provided an overview of the process, and
272 further clarified the definition of EDC to be used. The Endocrine Society defines EDCs
273 somewhat differently than the European Union, as an exogenous chemical, or mixture of
274 chemicals, that can interfere with any aspect of hormone action(3). Because of the EU decision
275 making context, panelists were advised to adhere to the EU definition, but to add a further
276 requirement that the chemicals interfere with hormone action (as elaborated in the Endocrine
277 Society definition).

278

279 Panels began by selecting the association for which the evidence was judged to be the strongest
280 to promote familiarity in subsequent iterations. For each exposure-outcome association, the
281 process in each group began with presentation of epidemiologic and toxicologic reviews of the
282 literature, and discussing the approach to identifying the overarching issues in attributing
283 individual EDC exposures to the subject outcome. Expert panelists were then asked to provide
284 their opinion about strength of the epidemiologic and toxicologic evidence for the exposure-
285 outcome relationship, and the nature of that relationship. Responses were submitted to the leader
286 anonymously.

287

288 Each leader then provided a summary of the findings from initial questionnaires and reasons for
289 the judgments. Panelists were encouraged to refine their answers anonymously in light of replies
290 of other experts on the panel, with a goal of convergence towards a consensus in subsequent
291 rounds of questionnaires. Panelists were advised to consider the Smith *et al* definition of AF, i.e.,
292 "the percentage of a particular disease category that would be eliminated if environmental risk
293 factors were reduced to their lowest feasible concentrations."⁽²⁹⁾ Recognizing that naturally
294 occurring EDCs in the environment such as phytoestrogens do exist, the steering committee
295 encouraged estimation of AFs attributable to anthropogenic activities, recognizing that naturally
296 occurring exposures (e.g., phytoestrogen exposure from soy milk) may also contribute.⁽⁴⁷⁾
297 Panelists were asked to focus on EU populations, identifying the population affected (including
298 age and demographic subgroups) as part of their iterative process, in addition to the population in
299 which the outcome is being assessed. They were asked to consider the reality of mixtures and
300 complexity of attribution in that context.

301

302 Management of ongoing discussions and trigger of subsequent rounds of questionnaires were
303 determined by the expert panel leads. Consistent with application of the Delphi method to
304 aspects of medical care,(45, 46, 48) pre-defined stop criteria included: a minimum of three
305 questionnaire rounds, achievement of majority consensus, and stability of results across rounds.
306 Converging answers for each EDC-outcome relationship formed the basis for manuscripts
307 accompanying this overview, which describe each expert panel process and were prepared by the
308 expert panel leads in collaboration with the other members after the meeting. Throughout the
309 Delphi process, the panels were strongly encouraged to produce ranges that represent low and
310 high bounds for the dose-response relationship, and to evaluate potential non-linearity and non-
311 monotonicity as well as presence or absence of threshold effects when appropriate. **Non-**
312 **monotonicity did not influence strength of evidence when supported in its biological plausibility,**
313 **though it could yield differences in the estimated disease burden.** While unanimity was
314 encouraged, in the event of non-unanimity, the range of strength of evidence evaluations from all
315 participants was input to develop a range of results for probability of causation.

316

317 *General Approach to Economic Estimation*

318

319 We applied a human capital approach(49, 50), which is currently the most widely used method to
320 calculate the costs of illness (51, 52). This approach measures the value of resources foregone and
321 output lost due to illness, such as lost earnings or household contributions as a homemaker, and
322 costs of medical treatment. With this method, costs were divided into direct and indirect costs. In

323 calculating these costs, we followed the widely cited costing guidelines recommended by the Panel
324 on Cost Effectiveness and Medicine(53). Direct costs are the value of resources that could be
325 allocated to other uses in the absence of disease. These include expenditures for hospitalization,
326 physician services, nursing home care, medical appliances, and related items. Indirect costs are the
327 value of the lost output of workers and retirees suffering premature death or disability. We
328 assumed the societal perspective, as opposed to the perspective of the health care payer, (54) and
329 our measures of costs adhered as closely as possible to the economic definition of costs, where cost
330 is represented by foregone opportunities.

331

332 Whenever possible, we utilized European data sources for cost-of-illness inputs, and relied upon
333 already published estimates when available. Our preference was to identify incremental costs
334 associated with a condition, rather than average costs, as these tend to produce overestimates
335 (55). When European data were not available, we extrapolated from available US estimates,
336 applying a correction factor representing the ratio of the per capita gross domestic product
337 purchasing power parity of each European country compared to the United States. All results are
338 presented in 2010 Euros, and represent costs as estimated to occur in 2010, the most recent year
339 for which prevalence/incidence data could permit robust estimation.

340

341 Finally, recognizing that attributable cost estimates were accompanied by a probability, we
342 performed a series of Monte Carlo simulations to produce ranges of probable costs across all the
343 exposure-outcome relationships, assuming independence of each probabilistic event. Separate
344 random number generation events were used to assign (1) causation or not causation, and (2) cost

345 given causation, using the base case estimate as well as the range of sensitivity analytic inputs
346 produced by the expert panel. To illustrate with an example, for an exposure-outcome
347 relationship with an 80% probability of causation, random values between zero and one in each
348 simulation led to the first step, which either assigned no costs (random value $\leq .2$) and costs
349 (random value $> .2$). For relationships in which lower and/or higher bound estimates of costs
350 were identified in addition to base case costs, a second random number generation was used to
351 assign costs in the scenario of causation. For those relationships with a lower and outer bound
352 estimate, equal probabilities were assigned to values below and above the base case estimate,
353 with costs linearly interpolated across the remaining probability range. For relationships for
354 which only a higher or lower bound estimate was available, a 50% probability was assigned for
355 the base case estimate, while the remaining 50% probability was applied over the range of the
356 higher/lower bound.

357

358 Recognizing that probability of causation could be highly influential on cost estimates, we
359 performed three sets of 1000 simulations, using the midpoints of the ranges for probability of
360 causation for each exposure-outcome relationship as a base case scenario, and low and high
361 bounds of the probability range as alternate scenarios, to assess the sensitivity of Monte Carlo
362 simulations to this input. For each of the three sets of simulations, we produced ranges of burden
363 and disease costs associated with EDCs. We developed a 95% confidence interval as well as the
364 interquartile range and first and ninth deciles to convey the spread of possible scenarios.

365

366 **Results**

367

368 Expert panels achieved consensus for probable (>20%) EDC causation for IQ loss and associated
369 intellectual disability; autism; attention deficit hyperactivity disorder; childhood obesity; adult
370 obesity; adult diabetes; cryptorchidism; male infertility and mortality associated with reduced
371 testosterone (Table 4). Only for testicular cancer was 0-19% probability of causation identified.
372 We refer the reader to accompanying manuscripts which describe specific results from each of
373 the expert panels (56-58), but to illustrate we present burden of disease results from a few
374 examples here.

375

376 The neurodevelopment panel estimated a strong probability (70-100%) that, each year in Europe,
377 13.0 million IQ points are lost (sensitivity analysis: 4.24-17.1 million) due to prenatal
378 organophosphate exposure, and 59,300 additional cases of intellectual disability (sensitivity
379 analysis: 16,500-84,400). With more modest probabilities, 316 cases of autism and 19,400-
380 31,200 new cases of ADHD annually are attributable to EDCs (sensitivity analysis: 126-631).

381 The male reproductive panel identified male infertility attributable to phthalate exposure to have
382 a 40-69% probability of causing 618,000 additional assisted reproductive technology procedures
383 annually in Europe. A 40-69% probability of lower testosterone concentrations in 55-64 year old
384 men due to phthalate exposure was identified, with 24,800 associated deaths annually. The
385 obesity/diabetes panel identified a 40-69% probability of phthalate exposure causing 53,900
386 cases of obesity and 20,500 new-onset cases of diabetes in older women annually. Prenatal BPA
387 exposure was identified to have a 20-69% probability of causing 42,400 new cases of childhood
388 obesity annually, with associated lifetime costs of €1.54 billion.

389

390 The most substantial costs were related to loss of IQ and intellectual disability attributable to
391 prenatal organophosphate exposure; base case estimates identified €146 billion in attributable
392 costs, while sensitivity analyses suggested that costs might actually range from €46.8-195 billion
393 annually. Phthalate attributable adult obesity was the second largest driver of costs, at €15.6
394 billion per year. The total costs of all conditions probably attributable to EDCs were €191
395 billion, with sensitivity analyses suggesting costs ranging from €81.83-269 billion annually.

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397 Accounting for probability of causation, the base case Monte Carlo simulation using the
398 midpoint of each range for probability of causation produced costs between €3.32.5-244-239
399 billion annually across the 1000 simulations (median, €157 billion; Figure 1). Using the 2010
400 EU purchasing-power-parity corrected Gross Domestic Product (GDP) estimate of €127.9

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401 billion(59), the estimated costs comprise 1.23% of GDP. There is a 5% probability that costs of
402 EDC exposures are less than €2021.6-3 billion annually, a 90% probability that costs are at least
403 €32.4-0 billion, a 75% probability that costs are at least €9665.4-6 billion/year, a 25% probability
404 of costs at least €194 billion/year, and a 10% probability of costs over €211-212 billion/year.

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406 Notably, using the lowest end of the probability range for each relationship in the Monte Carlo
407 simulations produced a range of €24.644.0 million-236-235 billion (median, €119-109 billion)
408 that differed modestly from the base case probability inputs. There is a 5% probability that costs
409 of EDC exposures are less than €810.8-0 billion annually, a 90% probability that costs are at
410 least €15.6-8 billion, a 75% probability that costs are at least €3130.9-8 billion/year, a 25%
411 probability of costs at least €179-181 billion/year, and a 10% probability of costs over €202-204
412 billion/year. Applying the lowest end of the probability range and assuming all the relationships

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413 are independent, multiplying each of the probabilities for the exposure-outcome relationships
414 suggests a very high (>99% =1-0.3x0.3x0.6x0.8x0.6x0.6x0.8x0.6x0.6x0.6x0.6x0.8x0.8)
415 probability that EDCs contribute to disease in Europe. Leaving aside the highly probable costs of
416 developmental neurotoxicity from organophosphate pesticide and brominated flame retardants,
417 there is still a substantial probability (>98%) that one or more of the other exposure-outcome
418 relationships are causal. Using the highest end of the probability ranges narrowed the range of
419 costs more substantially (€6217.76-246 billion; median €176-180 billion). There was a
420 1021.80% probability of costs under €100 billion, and a 2831.95% probability of costs over €200
421 billion.

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423 Discussion

424

425 The primary finding of this manuscript is that there is a substantial probability of very high
426 disease costs across the lifespan associated with EDC exposure in the European Union. For
427 some perspective, the median €157 billion cost/year we identified is approximately one sixth the
428 €798 billion European cost of brain disorders in 2010 (60), and 1.23% of GDP. These costs will
429 accrue annually insofar as exposures that are harmful continue unabated. Thus, regulatory action
430 to limit exposure to the most widely prevalent and potentially hazardous EDCs is likely to
431 produce substantial economic benefits. These economic benefits should inform decision-making
432 on measures to protect public health.

433

434 Calculations of the health and economic benefits associated with reducing exposure to
435 environmental chemicals have proven extremely informative to regulatory decision-making.

436 Estimates of the benefits associated with removal of lead-based paint hazards informed funding
437 of federal lead hazard control grants in the early 2000s (61), and measurement of the benefits
438 associated with reduced prenatal methylmercury toxicity (62) informed formulation of the global
439 mercury treaty. Though analyses like these are highly valuable, they have been typically limited
440 to associations where causation is certain. Decades of epidemiologic data typically are required
441 before possible causation has been acknowledged and attributable disease burden calculated (63,
442 64). Failure of the current approach in assessing the economic costs of environmental health
443 hazards is especially acute for EDCs, for which longitudinal studies of early life exposures are
444 only beginning to be completed. The approach we have taken will potentially transform decision
445 making in environmental health, by providing a new model for evaluating environmental health
446 risks and permitting a complete assessment of the potential costs of failing to prevent chronic
447 disease through use of safer alternatives to EDCs. It produces substantial insights regarding
448 strength of the epidemiologic and toxicologic data, placing them alongside the cost of the disease
449 as never done before. This approach also documents data gaps in both the epidemiology and
450 toxicology of EDCs, which has only been documented through systematic reviews.

451
452 We used an expert elicitation approach to estimating the probability that EDCs contribute to
453 disease and disability. While the Global Burden of Disease project does rely on expert opinion,
454 it has focused on a small subset of exposure-outcome relationships with the strongest causation.
455 In preparation for this work, we considered the International Agency for Research and Cancer
456 (65) and World Cancer Research Fund grading systems (66), but these approaches could not be
457 readily adapted to account for contribution by an endocrine disruptor mechanism for this project.

458

459 Expert opinion is of course not a substitute for solid epidemiologic evidence regarding the
460 relationships between EDCs and disease, or for systematic toxicological documentation
461 regarding endocrine disruption as the mechanism by which EDCs act to promote disease. Yet,
462 uncertainty is a reality across aspects of decision-making in science and public policy, and we
463 relied upon widely accepted and used methods for accounting for uncertainty.(32) In the course
464 of a two-day workshop and associated conference calls, the panels could not be comprehensive
465 in their examination of the panorama of EDCs and potential effects. While each accompanying
466 manuscript endeavors to call attention to the limited scope of the chemicals and outcomes
467 assessed, it bears emphasis that the present work focused only on the conditions and exposures
468 with the strongest evidence for causation, within the three disease areas for which the steering
469 committee judged the investment in assembling an expert panel to be appropriate.

470
471 In addition to producing ranges of probability of causation based upon strength of evidence, we
472 also endeavored to incorporate the substantial uncertainty in EDC-disease relationships using
473 sensitivity analyses to model impacts of key uncertainties on estimates of burden of disease and
474 costs that produced a wide range of potential costs associated with EDCs. The estimates
475 presented in this report are uncertain, and the range of likely costs has been expressed as allowed
476 by the evidence available. Clearly, more research would allow calculation of better estimates, but
477 would take time and substantial investment. Given the current concerns about regulation of
478 endocrine disruptors, the present report aims at providing the best possible documentation for
479 possible decision-making at this time. Though the analysis was limited to the EU, if similar
480 exposures and effects are identified in the US and other areas of the world, then the burden of
481 disease and costs attributable to EDCs elsewhere is likely to be on the same order of magnitude.

482 Additional investment across the world in research to identify how and which EDCs are harmful
483 is also indicated.

484

485 Three additional issues should be considered when evaluating our findings. First, the approach
486 we took to quantifying the probability of costs fails to account for risk aversion. Generally,
487 societies value small probabilities of costs (e.g., 10% of \$1,000) more than the weighted average
488 ($\$100 = (10\% \times \$1,000) + (90\% \times \$0)$). A major driver for health insurance is that people may
489 value investment on behalf of preventing even a rare but uncertain outcome more than the
490 weighted-average likelihood of the consequences of the outcome. Because people generally
491 prefer to pay more in such a scenario, societies are described as risk-averse (67). We did not
492 account for risk aversion in the present work. Indeed, the societal value of the uncertain health
493 effects analyzed here may be much higher than our calculations. Second, cost-of-illness
494 approaches fail to capture the complete scope of economic costs associated with illness
495 (especially psychological and other indirect or intangible costs that are difficult to assess), thus
496 our cost-of-illness estimate of EDCs must be considered an underestimate (68-71). Finally,
497 when considering the costs of safer alternatives, it is important to keep in mind that estimates of
498 the cost of safer alternatives produced by those who create environmental toxicants may
499 overestimate costs of prevention because they do not account fully for ongoing technological
500 innovation that may reduce future costs of safer alternatives (72). The costs of such innovations
501 are often one-time costs, whereas the benefits of prevention accumulate over time, as has been
502 documented with the annual economic benefit of eradicating lead from gasoline (73).

503

504 Finally, the findings described here suggest potentially large burdens of disease and associated
505 costs in the developed world, insofar as exposures are similar. Future studies could extend and
506 apply this approach to the United States, where the National Health and Nutrition Examination
507 Survey among other studies offer arguably more comprehensive and national reference points for
508 extrapolation. In the industrializing world, the attributable disease burden and costs could well
509 be higher in a much weaker regulatory framework (74). A major challenge to documenting the
510 scope of EDC-attributable disease in these more vulnerable populations is the absence of
511 biomarker or other exposure data to support similar estimates. The World Health Organization
512 and United Nations Environment Programme can catalyze and coordinate such efforts, which
513 will require substantial resources for its proper execution.

514

515

516 **Table 1.** Framework for Evaluating Probability of Causation.

Epidemiologic Evaluation \ Toxicologic Evaluation	Toxicologic Evaluation		
	Strong (Group 1)	Moderate (Group 2A)	Weak (Group 2B)
High	Very High (90-100%)	High (70-89%)	Medium (40-69%)
Moderate	High (70-89%)	Medium (40-69%)	Low (20-39%)
Low	Medium (40-69%)	Low (20-39%)	Very Low (0-19%)
Very Low	Low (20-39%)	Very Low (0-19%)	Very Low (0-19%)

517

518 Adapted from (32).

Table 2.Criteria for Evaluating Epidemiologic Evidence.

Quality of evidence	Interpretation	Study design	Lower the quality in presence of	Raise the quality in presence of
High	We are very confident that the true effect lies close to that of the estimate of the effect.	Randomized trial	<p>Study limitations: -1 Serious limitations -2 Very serious limitations</p> <p>-1 Important inconsistency</p> <p>Directness: -1 Some uncertainty -2 Major uncertainty</p> <p>-1 Imprecise data</p> <p>-1 High probability of reporting bias</p>	<p>Strong association: +1 Strong, no plausible confounders, consistent and direct evidence +2 Very strong, no major threats to validity and direct evidence +1 Evidence of a dose-response gradient +1 All plausible confounders would have reduced effect</p> <p>Additional criteria (applied across a body of evidence based on multiple study designs) : +1 Consistency across multiple studies in different settings +1 Analogy across other exposure sources</p>
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	Quasi-experimental (with controls) and before and after (uncontrolled) studies		
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect	Observational study		
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect	Any other evidence		

Adapted from (33, 75).

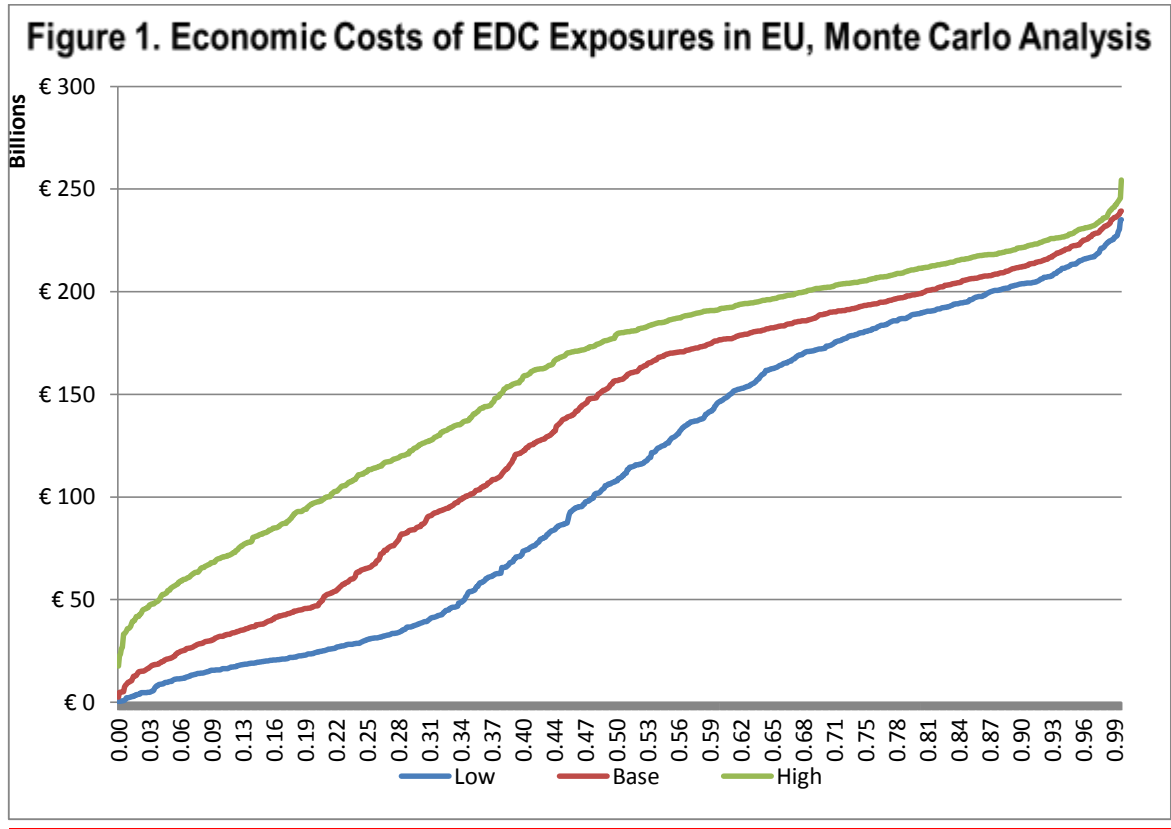
Table 3. Criteria for Evaluating Toxicologic Evidence.

Quality of evidence	Interpretation	Study design
Strong, Group 1 (Endocrine disruptor)	There is a strong presumption that the chemical has the capacity to cause the health effect through an endocrine disruptor mechanism.	The animal studies provide clear evidence of the ED effect in the absence of other toxic effects, or if occurring together with other toxic effects, the ED effects should not be a secondary non-specific consequence of other toxic effects. However, when there is e.g. mechanistic information that raises doubt about the relevance of the effect for humans or the environment, Group 2 may be more appropriate. Substances can be allocated to this group based on: <ul style="list-style-type: none"> •Adverse <i>in vivo</i> effects where an ED mode of action is plausible •ED mode of action <i>in vivo</i> that is clearly linked to adverse <i>in vivo</i> effects (by e.g. read-across)
Moderate, Group 2a (Suspected endocrine disruptor)	There is some evidence from experimental animals, yet the evidence is not sufficiently convincing to place the substance in Group 1.	The health effects are observed in the absence of other toxic effects, or if occurring together with other toxic effects, the ED effect should be considered not to be a secondary non-specific consequence of other toxic effects. Substances can be allocated to this group based on: <ul style="list-style-type: none"> •Adverse effects <i>in vivo</i> where an ED mode of action is suspected •ED mode of action <i>in vivo</i> that is suspected to be linked to adverse effects <i>in vivo</i> •ED mode of action <i>in vitro</i> combined with toxicokinetic <i>in vivo</i> data (and relevant non test information such as read across, chemical categorisation and QSAR predictions)
Weak, Group 2b (Potential endocrine disruptor)	There is some evidence indicating potential for endocrine disruption in intact organisms.	There is some <i>in vitro</i> / <i>in silico</i> evidence indicating a potential for endocrine disruption in intact organisms or effects <i>in vivo</i> that may, or may not, be ED-mediated.

Adapted from (36).

Table 4. Evaluations of Exposure-Outcome Relationships.

Exposure	Outcome	Strength of Human Evidence	Strength of Toxicologic Evidence	Probability of Causation	Base estimate	Low estimate	High estimate
Polybrominateddiphenyl ethers (PBDE)	IQ Loss and Intellectual Disability	Moderate-to-high	Strong	70-100%	€ 9,587,571,420	€ 1,577,449,522	€ 22,356,864,892
Organophosphate pesticides	IQ Loss and Intellectual Disability	Moderate-to-high	Strong	70-100%	€ 146,178,556,566	€ 46,760,988,423	€ 194,850,545,761
Dichlorodiphenyltrichloroethane (DDE)	Childhood obesity	Moderate	Moderate	40-69%	€ 24,610,041	€ 24,610,041	€ 86,448,264
Dichlorodiphenyltrichloroethane (DDE)	Adult diabetes	Low	Moderate	20-39%	€ 834,741,170	€ 834,741,170	€ 16,694,823,393
Di-2-ethylhexylphthalate (DEHP)	Adult obesity	Low	Strong	40-69%	€ 15,610,612,091	€ 15,610,612,091	€ 15,610,612,091
Di-2-ethylhexylphthalate (DEHP)	Adult diabetes	Low	Strong	40-69%	€ 606,944,344	€ 606,944,344	€ 606,944,344
Bisphenol A	Childhood obesity	Very low-to-low	Strong	20-69%	€ 1,537,177,463	€ 1,537,177,463	€ 1,537,177,463
Polybrominateddiphenyl ethers (PBDE)	Testicular cancer	Very low-to-low	Weak	0-19%	€ 847,975,932€ 1,695,951,864	€ 313,179,835€ 626,359,671	€ 847,975,932€ 1,695,951,864
Polybrominateddiphenyl ethers (PBDE)	Cryptorchidism	Low	Strong	40-69%	€ 129,807,327€ 259,614,654	€ 116,841,584€ 233,683,168	€ 129,807,327€ 233,683,168
Benzyl and butylphthalates	Male Infertility, Resulting in Increased Assisted Reproductive Technology	Low	Strong	40-69%	€ 4,714,114,146	€ 4,714,114,146	€ 4,714,114,146
Phthalates	Low testosterone, Resulting in Increased Early Mortality	Low	Strong	40-69%	€ 7,958,358,238	€ 7,958,358,238	€ 7,958,358,238
Multiple exposures	ADHD	Low-to-moderate	Strong	20-69%	€ 1,743,332,686	€ 1,212,298,027	€ 2,861,405,410
Multiple exposures	Autism	Low	Moderate	20-39%	€ 199,339,876	€ 79,735,951	€ 398,679,753



The numbers on the X-axis denote cumulative probability across the 1000 simulations for base case probability of causation, as well as low and high bounds for probability of causation.

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