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Title:

An approach to classifying occupational exposures to endocrine disrupting chemicals by sex hormone function using an expert judgement process

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Abstract

Endocrine disrupting chemicals (EDCs) are exogenous substances that interfere with the endocrine system and cause adverse effects. We aimed to classify the effects of 24 known EDCs, prevalent in certain occupations, according to four modes of action (estrogenic, anti-estrogenic, androgenic, and/or anti-androgenic).

A literature search, stratified into four types of literature was conducted (namely: national and international agency reports; review articles; primary studies; ToxCastTM). The state of the evidence of each EDC on sex hormone function was summarized and reviewed by an expert panel. For each mode of action, the experts evaluated the likelihood of endocrine disruption in five categories: “No”, “Unlikely”, “Possibly”, “Probably”, and; “Yes”.

Seven agents were categorised as “Yes,” or having strong evidence for their effects on sex hormone function (anti-androgenic: lead, arsenic, butylbenzyl phthalate, dibutyl phthalate, dicyclohexyl phthalate; estrogenic: nonylphenol, bisphenol A). Ten agents were categorised as “Probable,” or having probable evidence (anti-androgenic: bis(2-ethylhexyl)phthalate, nonylphenol, toluene, bisphenol A diisononyl phthalate; androgenic: cadmium, and; estrogenic: copper, cadmium). Two agents (arsenic, polychlorinated biphenyls) had opposing conclusions supporting both “probably” estrogenic and anti-estrogenic effects.

This synthesis will allow researchers to evaluate the health effects of selected EDCs with an added level of precision related to the mode of action.

Keywords: endocrine disruptor, estrogenic, anti-estrogenic, androgenic, anti-androgenic, occupational exposures

1. Background

Public concern about the impact of endocrine disrupting chemicals (EDCs) on both humans and the environment is growing steadily. EDCs are exogenous substances that cause adverse health effects through interference with the endocrine system; exposure occurs through occupational, dietary and environmental sources, with food being the major route of exposure for many EDCs (1, 2). However, a comparison of reported biomarker levels of selected EDCs revealed that concentrations of these chemicals are between 9 to 45 times higher in occupationally-exposed workers than in the general population (1, 3-7), making this an important and more easily definable target population for study.

There is growing evidence that EDCs may affect fertility (8-11) and the progression of some diseases like obesity, endometriosis and some cancers (8, 12, 13). The disruption of sex hormone homeostasis (14) has been associated with the risk of sex-specific cancers, including: breast and prostate cancers (15, 16), and possibly endometrial and ovarian cancers (17, 18). The incidence of colorectal cancer differs by sex (19), and accumulating epidemiologic evidence shows that exposure to certain female sex hormones is associated with a lower risk of colorectal cancer (20-23).

The main mechanisms of action through which EDCs may disrupt the endocrine system have been previously detailed by Cambarnous (24); they include: 1) inhibiting and/or mimicking the effect of hormones; 2) disrupting the production, metabolism and transport of hormones and; 3) disrupting the production of hormone receptors (25). Pertinent to sex hormones, these effects can be further characterised as: estrogenic (promotes the biosynthesis of estrogens or mimics the physiologic activity of estrogens) (26), anti-estrogenic (inhibits the biosynthesis or physiologic activity or biological effects of estrogens)(27), androgenic (promotes the biosynthesis of androgens or mimic the physiologic activity of androgens) (28) and/or anti-androgenic (inhibits the biosynthesis or physiologic activity or biological effects of

androgens) (29).

Several researchers have suggested a possible cumulative effect of exposure to multiple EDCs (30-35). Evaluation of these combined effects will be greatly enhanced by taking into account these different modes of action in the assessment of health risks. A consensus statement by La Merrill *et al.*(36) is one of the most notable recent endeavours to address this issue. A key characteristics framework was developed to search, organize and evaluate mechanistic evidence to support the identification of EDCs. This framework was applied to bisphenol A, diethylstilbestrol and perchlorate and helps to integrate data across a vast literature of mechanistic studies to help identify EDC hazards. Other endeavors, have been more directed and specific; Bonde *et al.* (37) conducted a systematic review and meta-analysis to systematically synthesize published data on the risk of cryptorchidism, hypospadias, low sperm count and testicular cancer following in utero or infant exposure to suspected EDCs.

Within the context of an epidemiological study currently being conducted to assess occupational exposure to EDCs and colorectal cancer risk within a large Canadian prospective cohort study (Canadian Partnership for Tomorrow Project – CPTP), we reviewed the literature to identify evidence that can be used by experts to classify the effects of known EDCs more precisely as estrogenic, anti-estrogenic, androgenic and/or anti-androgenic. The purpose of this endeavour is ultimately aimed to inform future conceptualization of exposure to EDCs, via modes of action, that may have different impacts on disease etiologies.

2. Methods

2.1 Identification of EDCs for the current review

In the epidemiologic study being conducted to assess occupational exposure to EDCs and colorectal cancer risk, occupational exposures to EDCs are assessed using the Canadian Job Exposure Matrix (CANJEM) (38). Briefly, CANJEM provides Canadian-relevant

information on the probability, frequency and intensity of exposure to a list of 258 agents for a given job code in a specific time period. To identify which agents present in CANJEM would comprise the EDCs of interest for this review, we cross-matched the list of CANJEM agents to those chemicals, irrespective of the mode of action, that have been identified as EDCs or potential EDCs, by the European Commission following a thorough scientific assessment (available at: http://ec.europa.eu/environment/archives/docum/pdf/bkh_annex_13.pdf). A second source, an EDC-JEM (39), defined distinct classes of substances that represent the majority of EDCs found in workplaces. Briefly, using a list of substance with potential endocrine disrupting potency established from a literature review, three occupational hygienists independently assigned exposure scores to occupations. From these two sources, 26 potential EDCs of interest were selected for review.

2.2 Literature search strategy

In order to provide a body of evidence for the expert panel to classify the most likely mode(s) of action of each potential EDC as estrogenic and/or, anti-estrogenic and/or, androgenic and/or anti-androgenic, a literature search stratified into 4 tiers was conducted.

In Tier 1, national and international agency reports, which encompassed evaluations of published *in vitro*, *in vivo* and/or data from an intact organism (including humans), were prioritized. The literature search was conducted in Google using a combination of keywords “substance name” and “endocrine effect” (40-50). Any definitive conclusions on the presence or absence of (anti-)estrogenic or (anti-)androgenic effects were summarized and the agent was not further reviewed in Tiers 2 and 3. If the conclusions regarding any of the four effects from the report were qualified (e.g. "estrogenic effect cannot be excluded"), this specific effect was included in Tier 2 for evaluation. If no such report was identified for a given agent, a Tier 2 review was carried out.

In Tier 2, the PubMed database was used to identify published review articles and meta-analysis articles. The combination of keywords used was: "substance name" and "androgen" or "estrogen" or "endocrine effect". A time constraint was applied only for substances for which a report was found in Tier 1 but the conclusions of the report were qualified; in this case, only review articles published after the report were considered (51-57). The objective of the literature search was similar to that used in Tier 1, to identify conclusions regarding the possible estrogenic, anti-estrogenic, androgenic and/or anti-androgenic effect. Again, if no review was found or no firm conclusions were stated in the review for a given agent, it was included in the Tier 3 review.

In Tier 3, the PubMed database was used to identify primary research studies conducted *in vitro*, *in vivo* or in humans. Two search strategies were used. First, using the systematic reviews identified in Tier 2, we identified the original studies and abstracted information on their methods and results (58-136). Second, for the EDCs that were not have a systematic review, we conducted our own review using the combination of keywords: "substance name" and for:

- effects related to estrogenic or anti-estrogenic ((anti-)estrogenic) effects: "estrogen receptor" or "estrogen levels" or "aromatase (CYP19)"
- effects related to androgenic or anti-androgenic ((anti-)androgenic) effects: "androgen receptor" or "testosterone levels" or "PPAR γ " or "INSL3"
- effects on enzymes and hormones that can impact estrogen and androgen levels: "CYP17" or "17beta-HSD" or "5alpha reductase" or "FSH" or "LH";

where CYP19, PPAR γ , INSL3, CYP17, 17beta-HSD, 5alpha reductase are enzymes or hormones involved in the development of male and female fertility(137-143). These keywords were selected to ensure a broad capture of mechanistic studies that may have examined the

potential for endocrine disruption of our selected EDCs but not have included “endocrine effects” in their keywords.

In Tier 4, to complement our literature search strategy in Tiers 1 to 3, we used the US-Environment Protection Agency (EPA) Toxicity Forecaster (144). ToxCastTM uses high-throughput screening methods and computational toxicology approaches to rank and prioritize chemicals. We searched the ToxCastTM database to identify the bioactivity profiles of our 26 EDCs of interest in relation to estrogen receptor and androgen receptor activity.

2.3 Expert Evaluation

Three members of the team (R. Prichystalova, E. Caron-Beaudoin and E. Dirksen with expertise in Occupational and Process Safety, Biology, and Biomedical sciences, respectively) reviewed the literature in relation to 24 of the 26 potential EDCs of interest; no literature on the possible (anti-)estrogenic or (anti-)androgenic effects was found for octachlorostyrene and phenol isooctyl. Based on the literature reviews conducted in Tiers 1 to 4, the available evidence was summarised for the 24 remaining potential EDCs (see Supplementary Materials). Subsequently, an expert panel consisting of seven experts with experience in endocrine disruption, spanning the fields of toxicology, environmental sciences and epidemiology was assembled. The expert panel was tasked with individually reviewing the evidence and categorizing the likelihood for each EDC to affect estrogenic, anti-estrogenic, androgenic and/or anti-androgenic activity. All 24 EDCs were reviewed by two experts independently, with each expert reviewing between six to eight summaries. Specifically, for each of the four effects, the experts were asked to evaluate activity, based on the following categories:

- “No” (there is no or very little evidence suggesting there is such an effect),
- “Unlikely” (it is more likely than not that there is no such effect),
- “Possibly” (there is equal evidence for and against such an effect),
- “Probably” (it is more likely than not that there is such an effect) and,

- “Yes” (there is strong evidence suggesting such an effect).

Any differences in assessment between the two reviewers for a given EDC were reconciled as follows. Where the evaluations provided by each expert differed by one level (e.g. if expert 1 concluded “No” while expert 2 concluded “Unlikely”) then the more conservative conclusion was taken (i.e. in the above scenario, “No” would be the conclusion). In case there was any discordance by more than one level (e.g. if expert 1 concluded “No” while expert 2 concluded “Possibly”), then a third expert was asked to review and assess the evidence (hereafter referred to as the “second round” of evaluations). The final assessment in this case was provided by the median assessment, which was either the middle or majority assessment. E.g. for carbon disulphide and its anti-androgenic effect: Expert 1 concluded “Yes,” Expert 2 concluded “Possibly” and Expert 3 concluded “Unlikely”; in this scenario, the final assessment was “Possibly” anti-androgenic effect.

3. Results

3.1. Summary of the Literature Synthesis

Table 1 summarizes the Tier 1 and 2 reviews of the 24 potential EDCs. Specifically, national and international agency reports were identified for nine substances in Tier 1 (bis(2-ethylhexyl phthalate, copper, bisphenol A, butylbenzyl phthalate, dibutyl phthalate, dicyclohexyl phthalate, diisodecyl phthalate, diisononyl phthalate, polychlorinated biphenyl). For (anti-)estrogenic effects, conclusive evidence was found in reports from Tier 1 for bisphenol A and polychlorinated biphenyl. For (anti-)androgenic effects, conclusive evidence was available from Tier 1 reports for bis(2-ethylhexyl) phthalate, bisphenol A, butylbenzyl phthalate, dibutyl phthalate, dicyclohexyl phthalate, diisononyl phthalate and polychlorinated biphenyl. For bisphenol A and polychlorinated biphenyl there was conclusive evidence found in Tier 1 for both (anti-)estrogenic and (anti-)androgenic effects.

For Tier 2, conclusive evidence from review articles on (anti-)estrogenic effects was found for nonylphenol and cadmium. Additionally, the evidence on (anti-)androgenic effects was available for aluminum and cadmium from Tier 2 reviews. Table 2 presents an overview of the primary research studies found as part of the Tier 3 review.

Finally, Table 3 presents the results of the bioactivity characterisation of our 24 potential EDCs using ToxCast in relation to estrogen and androgen receptor activity (Tier 4). For the majority of the substances, no data were found in ToxCast. In contrast, diethyl phthalate, bisphenol A, butylbenzyl phthalate, dibutyl phthalate, dicyclohexyl phthalate and phenol had data on their effects on the estrogen receptor. For the androgen receptor, data were found for diethyl phthalate, dibutyl phthalate, bisphenol A, dicyclohexyl phthalate and phenol.

3.2. Results of Expert Panel Evaluation

After the first round of expert evaluation, discordances (defined as differences in evaluations by more than one level) were found for 10 of the 24 potential EDCs for which a second round of evaluation was conducted. Figure 1 presents the final results from the expert panel evaluation for each agent. Similarly, Table 4 presents an alternative summary of the final conclusions reached by the expert panel for each agent. The major uses of each agent in the occupational setting are summarized in Table 5. Any discordances and the final conclusions reached for each agent are presented as follows.

Bis(2-ethylhexyl) phthalate

No discordance was found for any of the four effects. The experts concluded that bis(2-ethylhexyl) phthalate has possible estrogenic and probable anti-androgenic effects, but no anti-estrogenic and androgenic effects.

276 **Lead**

277 No discordance was found for any of the four effects. The experts concluded that lead
278 has possible estrogenic, probable anti-estrogenic and definite anti-androgenic effects, but no
279 androgenic effect.

280 **Arsenic**

281 Discordance between the first two experts on the anti-estrogenic effects of arsenic
282 necessitated a third expert review. After the second round of evaluations, the experts concluded
283 that arsenic has probable estrogenic, probable anti-estrogenic, unlikely androgenic and definite
284 anti-androgenic effects.

285 **Mercury**

286 No discordance was found for any of the four effects. The experts concluded that
287 mercury has possible estrogenic, unlikely anti-estrogenic and possible anti-androgenic effects
288 but no androgenic effect.

289 **Nonylphenol**

290 No discordance was found for any of the four effects. The experts concluded that
291 nonylphenol has definite estrogenic, unlikely androgenic and probable anti-androgenic effects,
292 but no anti-estrogenic effect.

293 **Copper**

294 No discordance was found for any of the four effects. The experts concluded that copper
295 has probable estrogenic and possible anti-androgenic effects, but no anti-estrogenic and
296 androgenic effect.

297 **Toluene**

298 There was discordance between the experts in the androgenic effects of toluene. After
299 the second round of evaluations, the experts concluded that toluene has possible anti-estrogenic
300 and probable anti-androgenic effects, but has no estrogenic and androgenic effects.

301 **Aluminum**

302 Discordances in the anti-estrogenic and anti-androgenic effects of aluminium were
303 found. After the second round of evaluations, the experts concluded that aluminium has possible
304 estrogenic, possible anti-estrogenic and possible anti-androgenic effects, but has no androgenic
305 effect.

306 **Diethyl phthalate**

307 No discordance was found for any of the four effects. The experts concluded that diethyl
308 phthalate has possible estrogenic and possible anti-androgenic effects, but has no anti-
309 estrogenic and androgenic effects.

310 **Styrene**

311 Discordance between the experts for the anti-androgenic effects was found. After the
312 second round of evaluations, the experts concluded that styrene has no anti-estrogenic,
313 estrogenic, anti-androgenic or androgenic effects.

314 **Bisphenol A**

315 No discordance was found for any of the four effects. The experts concluded that
316 bisphenol A has definite estrogenic, and probable anti-androgenic effects, but no anti-estrogenic
317 and androgenic effects.

318 **Butylbenzyl phthalate**

319 No discordance was found for any of the four effects. The experts concluded that
320 butylbenzyl phthalate has possible estrogenic and definite anti-androgenic effects, but has no
321 anti-estrogenic and androgenic effects.

322 **Cadmium**

323 No discordance was found for any of the four effects. The experts concluded that
324 cadmium has probable estrogenic and androgenic effects, but has no anti-estrogenic and anti-
325 androgenic effects.

326 **Carbon disulphide**

327 Discordance was found for the anti-estrogenic effects between the initial two experts
328 and thus, a third expert was invited to provide an evaluation. After the second round of
329 evaluations, the experts concluded that carbon disulphide has unlikely anti-estrogenic and
330 possibly anti-androgenic effects, but has no estrogenic and androgenic effects.

331 **Dibutyl phthalate**

332 Discordance for the anti-estrogenic effects necessitated a third expert review. After the
333 second round of evaluations, the experts concluded that dibutyl phthalate has possible
334 estrogenic, unlikely anti-estrogenic and definite anti-androgenic effects, but has no androgenic
335 effect.

336 **Dicyclohexyl phthalate**

337 Discordance was found for the androgenic effects between the two experts. After the
338 second round of evaluations, the experts concluded that dicyclohexyl phthalate has possible
339 estrogenic, possible anti-estrogenic and certain anti-androgenic effects, but has no androgenic
340 effect.

341 **Diisodecyl phthalate**

342 No discordances were found for the four effects. The experts concluded that diisodecyl
343 phthalate has unlikely androgenic effects, and no estrogenic, anti-estrogenic and anti-
344 androgenic effect.

345 **Diisononyl phthalate**

346 Discordances for both the estrogenic and androgenic effects were found between the
347 first two experts. After the second round of evaluations, the experts concluded that diisononyl
348 phthalate has unlikely estrogenic, unlikely anti-estrogenic, unlikely androgenic and probable
349 anti-androgenic effects.

350

351 **Ethylene glycol**

352 No discordances were found for the four effects. The experts concluded that ethylene
353 glycol has possible estrogenic, but has no anti-estrogenic, androgenic and anti-androgenic
354 effects.

355 **Polychlorinated biphenyls**

356 No discordances were found for the four effects. The experts concluded that
357 polychlorinated biphenyls have probable estrogenic, probable anti-estrogenic and possible anti-
358 androgenic effects, but have no androgenic effect.

359 **Perchloroethylene (also known as Tetrachloroethylene)**

360 No discordances were found for the four effects. The experts concluded that
361 perchloroethylene has no (anti-)estrogenic or (anti-)androgenic effects.

362 **Phenol**

363 No discordances were found for the four effects. The experts concluded that phenol has
364 no (anti-)estrogenic or (anti-)androgenic effects.

365 **Trichloroethylene**

366 Discordances were found for the (anti-)estrogenic and (anti-)androgenic effects in the
367 first round of evaluations. After the second round of evaluations, the experts concluded that
368 trichloroethylene has unlikely anti-estrogenic, unlikely androgenic and possible anti-
369 androgenic effects, and no estrogenic effect.

370 **Xylene**

371 Discordance between the first two experts for estrogenic effects necessitated a third
372 expert review. After the second round of evaluations, the experts concluded that xylene has
373 unlikely estrogenic effect, and no anti-estrogenic effects, androgenic and anti-androgenic
374 effects.

375

4. Discussion

4.1 Summary of our Literature Search and Expert Panel Evaluation

This review focused on classifying the effects of EDCs on sex hormones based on the current scientific evidence and expert opinion. In total, seven agents were categorised as having “strong” evidence for their effect on sex hormone function; where, five were classified as having an anti-androgenic mode of action (lead, arsenic, butylbenzyl phthalate, dibutyl phthalate and dicyclohexyl phthalate), and two as estrogenic (nonylphenol and bisphenol A). Four of these seven agents (nonylphenol, bisphenol A, dibutyl phthalate and dicyclohexyl phthalate) with “strong” evidence had Tier 1 and 2 evidence identified using our literature search strategy and thus, arguably had more data to be considered by the experts.

From the expert evaluation, ten of the reviewed agents were judged to have “probable” evidence to classify their effect on sex hormone function; two were classified as estrogenic (copper and cadmium), one as anti-estrogenic (lead), one as androgenic (cadmium), and five as anti-androgenic (bis(2-ethylhexyl)phthalate, nonylphenol, toluene, bisphenol A and diisonoyl phthalate). Two agents (arsenic and polychlorinated biphenyls) had conclusions supporting both “probably” estrogenic and anti-estrogenic effects. We identified literature within the Tier 1 and 2 search strategy for five of these ten agents with “probable” evidence (nonylphenol, bisphenol A, diisonoyl phthalate, cadmium, and polychlorinated biphenyls).

For styrene, phenol, xylene, perchloroethylene and diisodecyl phthalate the expert panel concluded that there is insufficient evidence for an effect on sex hormone function. Indeed, no literature was found in Tiers 1 and 2 regarding these agents (with the exception of diisodecyl phthalate). While in Tier 3, very few studies were found examining the effect of these agents (with the exception of styrene) on sex hormone pathways.

4.2 Utility of this Research

As workers in many industries are subject to concurrent exposure to several chemical contaminants, the combined health effects of such multi-exposures should not be overlooked. We conceptualized one approach to assess the health effects of endocrine disruption associated with occupational exposures via the categorization of agents according to their biological mode of actions on sex hormones. (36, 37, 145)

Within the context of an epidemiologic study investigating occupational exposures to EDCs, we posit that the different effects of EDCs on functioning of sexual hormones (i.e. estrogens and androgens) should be incorporated into risk analyses, given the growing literature supporting sex hormone imbalance in some cancer etiology. Phthalates and bisphenol A could be taken as an example where both agents are used within the production of plastic products. In these occupational settings, workers could be exposed to both substances concomitantly and it is difficult to predict the effect on endocrine disruption and/or subsequent health effects as bisphenol A likely operates through an estrogenic mode of action while phthalates (taken as a whole) are antagonists to androgens. Using our approach, we would consider both phthalates and bisphenol A separately to interrogate whether estrogenic versus anti-androgenic perturbations are more relevant for cancer development. In a similar manner, co-exposures to multiple EDCs with the same (anti-)estrogenic or (anti-) androgenic pathway could be summed into a total exposure when analysing exposure in relation to a health effect. For example, a worker exposed to both nonylphenol and bisphenol A, two chemicals with estrogenic effects may have higher risks associated with their co-exposures than another worker who is exposed to one or neither of the two agents. The objective of our review was to provide the backbone needed for such a synthesis of exposure profiles for analysis in future epidemiologic studies.

4.3 Limitations

Recent work by others has similarly put forth approaches to identify EDCs and integrate the literature on the hazards associated with exposure (36, 37, 145). Notably, the consensus statement by La Merrill *et al.* proposes ten key characteristics in which to support the identification of EDCs and systematically review the vast literature on EDC hazards; diethylstilbestrol, bisphenol A and perchlorate were used as examples to illustrate this approach. Broadly, this approach has the advantage of: identifying those chemicals which act upon the same key characteristics and, within a chemical, be useful for “connecting the dots” between different modes of action or adverse outcome pathways and/or identifying gaps in knowledge. We focused our review only on the effect of potential EDCs on perturbing sex hormone function; thus, effects on other endocrine pathways cannot be excluded. Applying the approach by La Merrill *et al.* could, in future, provide a more concerted and comprehensive overview of the state of knowledge of the chemicals under review.

Further, for some agents like arsenic, the experts found evidence supporting both estrogenic and anti-estrogenic effects. One important element in determining the likelihood of endocrine disruption in humans is the dose at which effects occurred in experimental models (cells, animals, humans). In the absence of dose / potency / exposure information, this review therefore is only a preliminary hazard assessment. However, as our review did not consider the impact of dose we cannot discuss the plausibility of this hypothesis. It is noteworthy that parallel efforts in computational biology are being made to identify and classify EDCs. Briefly, computational algorithms can be used to predict the activity of untested compounds with suspected endocrine disrupting properties (e.g. affinity to estrogen and androgen receptors), and prioritize those potentially active chemicals for future biological testing (146). Future evaluation efforts may consider integrating the predictive affinity of suspected EDCs, obtained

through these computation algorithms, as a way of standardizing the assessment of dose and adverse health effects.

Our approach was not a systematic attempt to capture all the available evidence for our selected EDCs for subsequent expert review. Though a four-tiered approach was developed to synthesize the evidence, we do not claim to have captured all possible mechanisms related to sex hormones disruption in our review. For example, sex hormone binding globulin, which influences hormone distribution, was not included as a keyword during our Tier 3 review. Nevertheless, with our chosen keywords, we posit that we would still capture the effect of altered hormone transport by the hormone plasma levels, including hormones like FSH and LH which are part of the feedback loops and regulate the production of steroid hormones like androgen and estrogen. Other potential mechanisms that our keywords did not target include epigenetic modifications in hormone-producing or hormone-responsive cells; hormone transport across cell membranes and; those which alters hormone metabolism or clearance. In addition, we did not use Medical Subject Headings while performing our search in Pubmed®; thus, we cannot exclude the possibility of having missed some published evidence. Further, we did not assess the quality of each study included in our review (e.g. the compliance of review articles with PRISMA guidelines), partly due to resource constraints but also that the use of evidence drawn from International and National bodies (Tier 1) and systematic reviews (Tier 2) assured already, a degree of quality. Nevertheless, particularly for the review of the literature in Tier 3, providing a completeness in reporting, as illustrated by Bonde *et al.*, could have an impact on the reliability of the conclusions reached by our experts.

Many of our agents of interest lacked sufficient evidence for expert evaluation. Indeed, this exercise highlighted a real need for more epidemiological and toxicological studies to extend the scientific knowledge base about the possible endocrine effects of these substances. Expert panels are useful when specialized opinion or conclusion is required for evaluation.

Generally, a greater variety of experts engaged in the evaluation based on various fields of expertise can have an impact on the final conclusions. The limitation of our expert panel was that it consisted of only seven experts and that each substance was reviewed by only two experts (or three in case of discordances); it can be presumed that the involvement of more experts would have increased the robustness of our conclusions.

5. Conclusion

International research efforts to better understand the presence of EDCs and related environmental effects have intensified over the past three decades and have led to an increasing level of concern and action on EDCs. To date, substantial efforts have been made by a wide variety of stakeholders across numerous sectors worldwide in identifying and categorizing EDCs. Overall this was an endeavour to summarize the current evidence concerning the effect of potential EDCs, common in the occupational environment, operating through either an estrogenic, anti-estrogenic, androgenic or anti-androgenic mode of action. The conclusions from this review could be used in concert with various occupational exposure assessment approaches like CANJEM to incorporate estimates of modes of action which would allow further hypotheses to be tested in epidemiological studies regarding multi-exposure to EDCs and health outcomes.

List of abbreviations

17 β -HSD - 17 beta-hydroxysteroid dehydrogenase
AR – Androgen receptor
CANJEM - Canadian Job Exposure Matrix
CPTP - Canadian Partnership for Tomorrow Project
CYP17 - Cytochrome P450 17 α Hydroxylase/17,20 Lyase

500 CYP19 - Aromatase cytochrome P450
501 EDC - Endocrine Disrupting Chemicals
502 ER – Estrogen receptor
503 FSH - Follicle-stimulating hormone
504 INSL3 - Insulin-like 3
505 JEM - Job Exposure Matrix
506 LH - Luteinizing hormone
507 PPAR γ - Peroxisome proliferator-activated receptors gamma
508 PVC - Polyvinyl chloride
509 ToxCast - Toxicity Forecaster
510 US-EPA – United States - Environmental Protection Agency

511
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519
520 **Conflict of Interest**

521 J. Hynes declared working relations with the styrene industry and users, thus, did not contribute
522 to the review on styrene. All other authors have no conflicts of interest to declare.

523

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