Occupational exposure to potential endocrine disruptors: further development of a job exposure matrix

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ABSTRACT

Objectives: The aim was to develop a new up-to-date and comprehensive job exposure matrix (JEM) for estimating exposure to potential endocrine disruptors in epidemiological research.

Methods: Chemicals with endocrine disrupting properties were identified from the literature and classified into 10 chemical groups: polycyclic aromatic hydrocarbons (PAHs), polychlorinated organic compounds, pesticides, phthalates, organic solvents, bisphenol A, alkylphenolic compounds, brominated flame retardants, metals and a miscellaneous group. Most chemical groups were divided into three to six subgroups. Focusing on the years 1996–2006, three experts scored the probability of exposure to each chemical group and subgroup for 353 job titles as "unlikely" (0), "possible" (1) or "probable" (2). Job titles with positive exposure probability scores were provided with exposure scenarios that described the reasoning behind the scores.

Results: Exposure to any chemical group was unlikely for 238 job titles (67%), whereas 102 (29%) job titles were classified as possibly (17%) or probably (12%) exposed to one or several endocrine disruptors. The remaining 13 job titles provided too little information to classify exposure. PAHs, pesticides, phthalates, organic solvents, alkylphenolic compounds and metals were often linked to a job title in the JEM. The remaining chemical groups were found to involve very few occupations.

Conclusions: Despite some important limitations, this JEM could be a valuable tool for exposure assessment in studies on the health risks of endocrine disruptors, especially when task specific information is incorporated. The documented exposure scenarios are meant to facilitate further adjustments to the JEM to allow more widespread use.

Endocrine disruptors have been described as exogenous substances that alter endocrine system functions and thereby cause adverse health effects.[1] Endocrine disruptors have been hypothesised to interfere with the fetal development of the male reproductive system.[2] More specifically, exposure in early gestation is believed to increase the risks of hypospadias and cryptorchidism (two birth defects in boys) and the risks of testicular cancer and male subfertility in adulthood. Besides disrupting male fetal development, endocrine disruptors are suspected of playing a role in the pathogenesis of various diseases, including endometriosis,[3] breast cancer[4] and prostate cancer.[5] However, the potential of current exposure levels to affect human health has been questioned by some researchers[6–8] and lacks detailed epidemiological evidence. Potential endocrine disruptors include a growing list of industrial chemicals, such as pesticides, dioxins and phthalates, but also synthetic hormones and naturally occurring phyto-oestrogens. Diet is probably the most important source of endocrine disruptors for the general population. Other sources include the environment, cosmetics and other consumer products.[1] In addition, relatively high exposure levels may occur in specific occupations.

In 2002, van Tongeren and colleagues published a job exposure matrix (JEM) for the assessment of occupational exposure to potential endocrine disruptors in the UK.[9] In this JEM, 348 job titles were linked to endocrine disruptor exposure probability scores: unlikely, possible or probable. A total of seven chemical groups were distinguished: pesticides, polychlorinated compounds, phthalates, alkylphenolic compounds, bi-phenolic compounds, heavy metals and a miscellaneous category. In constructing the JEM, three occupational hygienists independently assigned exposure scores to each of the occupations, after which consensus was reached. The JEM was developed in order to study the risk of hypospadias after maternal exposure to endocrine disruptors using data from the UK Office for National Statistics. Little evidence was found for an association between occupational exposure of the mother and hypospadias, although there was some indication for an increased risk when mothers were exposed to phthalates before adjustment for social class (OR 1.5; 95% CI 1.1 to 2.2) but not after (OR 1.3; 95% CI 0.8 to 2.0).[10] This JEM was also used in a Dutch case–control study investigating maternal and paternal risk factors for cryptorchidism and hypospadias. An increased risk of cryptorchidism was observed when fathers were exposed to pesticides according to the JEM (OR 3.8; 95% CI 1.1 to 13.4).[11]

Our objective was to use a similar JEM for exposure assessment of endocrine disruptors in another Dutch case–referent study on hypospadias and cryptorchidism, carried out at the Radboud University Nijmegen Medical Centre in 2005–2007. In this study, the parents of cases and referents provided data on job title, tasks and occupational exposures via postal questionnaires. The reason for extending the exposure assessment strategy with a JEM is that various potential endocrine disruptors, such as phthalates, metals and dioxins, are difficult to capture with questionnaires. Moreover, JEM exposure estimates are generally less influenced by recall bias as they are solely based on job titles, which are usually more reliably recalled than specific chemical exposures.[12] The validity of JEMs, however, has been shown to vary greatly from study to study and JEMs are unable to account for variability in exposures within occupations.[12] Additional difficulties may arise when a JEM is applied to populations different from that originally targeted.[13]

Dosemeci and colleagues demonstrated that the performance of a JEM could be considerably improved by efforts to obtain more accurate exposure estimates, in particular by (i) replacing dichotomous exposure scores (yes vs no) with exposure probabilities (low, medium, high), (ii) using a more suitable occupational classification scheme, and (iii) taking into account differences in exposures over time.[14] Kauppinen and colleagues pointed out that the applicability of a JEM could be improved by documenting the reasoning for the exposure scores, which would facilitate continuous improvement of the JEM and adjustments necessary for more widespread use.[15] In addition, studies performed by Kennedy *et al* and Semple *et al* indicate that the general problem of JEM exposure misclassification can be partly resolved by refining JEM exposure estimates with task specific information from questionnaires or interviews.[16 17]

Taking into account the above findings, our aim was to adjust the 2002 JEM for endocrine disruptors in order to improve its performance. This was motivated by the fact that the original JEM was based on a now outdated occupational classification and that some of the exposure probability scores were not valid for current working conditions due to changes in legislation. There was also a need to incorporate new knowledge on chemicals with endocrine disrupting properties in the JEM. Instead of the rather broad chemical groups in the original JEM, we made the new JEM more specific by assigning exposure probability scores for chemical subcategories. Furthermore, we decided to document the reasons for the exposure probability scores, which can be used to make further improvements or adjustments to the JEM and to facilitate refinement of the exposure scores with task specific information. With these modifications, we aimed to develop a new JEM that would allow a more accurate exposure assessment of endocrine disruptors to be used both in our case–referent study on hypospadias and cryptorchidism and in many other community based studies that involve occupational exposure to endocrine disruptors.

METHODS

The new JEM was developed according to the following general strategy in which the 2002 JEM was used as the starting point. First, chemicals with known or suspected endocrine disrupting properties were identified from the literature. Next, information was gathered about occupations at risk. The job titles in the original JEM were replaced by those from the UK Standard Occupational Classification 2000 (SOC2000).[18] Finally, exposure probability scores were revised or added by means of expert assessments and positive scores were accompanied by exposure scenarios that described the reasoning behind the scores. Table 1 summarises the specific characteristics of the new JEM. Like the original JEM, it is based on the UK situation, but an effort was made to focus the exposure probability scores on the 10 years before the expert assessments.

Table 1 Characteristics of the job exposure matrix

Selected chemicals	Evidence or indications for endocrine disrupting effects
	Relevant occupational exposure compared to other sources
Time frame	1996 to 2006
Focus population	Workers in the UK
Exposure scores	Exposure probability in three levels
	Assigned by means of expert assessments
	Do not reflect exposure level

In order to select potential endocrine disruptors for inclusion in the JEM, information was obtained from the report *Chemicals purported to be endocrine disruptors* by the Institute for Environment and Health in the UK,[19] the website www.ourstolenfuture.org by Colborn *et al*[20] and the World Health Organization report *Global assessment of the state-of-the-science of endocrine disruptors*.[1] Additional information was identified from research articles for which in some cases secondary literature sources were used. In selecting substances for the JEM, we considered whether occupational exposure was expected to contribute significantly to an individual's body burden in comparison to other sources of exposure such as diet, environment and consumer products. For that reason, phyto-oestrogens were not included in the JEM. This resulted in 10 chemical groups and 33 subgroups, which are displayed in table 2. The right hand column lists some reported properties for the chemical groups and subgroups that indicate their endocrine disrupting potential, but this should not be considered a complete overview.

Literature was then gathered about the occupational settings in which the selected chemicals are encountered. This reference material served as a tool for the expert assessment. The toxicological profiles of chemical substances listed by the US Agency for Toxic Substances and Disease Registry (ATSDR) were important literature sources,[47] as were the European Union risk assessment reports (EURAR) provided by the European Chemicals Bureau.[48] An effort was made to focus the reference material on the UK and on the time period from 1996 onwards. For example, information was obtained from the UK Chemicals Stakeholder Forum about current uses of alkylphenols and alkylphenol ethoxylates in various industries and about efforts to reduce human exposure and release in the environment in the past.[49] Additionally, the national pesticide registry was searched to identify the purposes of specific pesticides used in the UK.[50 51]

The 353 job titles in the SOC2000 were manually matched with the 348 job titles in the 2002 JEM, which were derived from the 1980 UK Categories of Occupations, so that the original exposure probability scores could be taken into account during the expert assessments. This was not possible for seven job titles that did not correspond with any job title in the original JEM.

A panel of three experts (MB, AH, MvT) assigned exposure probability scores for all chemical groups to each of the 353 job titles. Similar to the original JEM, the exposure probability scores were "unlikely", "possible" and "probable" (table 3). In addition, an "unclassifiable" score was assigned to job titles which were very broad and non-specific. For many chemicals, most people experience a certain level of exposure through diet, environment or widely used consumer products. The JEM exposure score refers to the probability that the occupational exposure level exceeds this background level in the general population. For example, exposure to polycyclic aromatic hydrocarbons (PAHs) may result from environmental tobacco smoke and traffic exhaust fumes, sources that affect most people at some level. Therefore, only full-time occupational exposure to PAHs from indoor tobacco smoke was considered in the JEM and positive exposure scores associated with traffic exhaust fumes only applied to workers who spend nearly all of their time driving or working outside on or beside a busy road.

Table 2 Chemical groups and subgroups of substances with endocrine disrupting potential that were selected for the job exposure matrix

Chemical group	Subgroups	Description	Reported endocrine disrupting effects
1. Polycyclic aromatic hydrocarbons	None	Formed by incomplete combustion of carbon-containing fuels Constituents in tar	Anti-oestrogenic effects in vitro[21]
2. Polychlorinated organic compounds	2.1 Polychlorinated biphenyls (PCBs) 2.2 Dioxins, furans, polychlorinated naphthalene (PCN) 2.3 Hexachlorobenzene (HCB) 2.4 Octachlorostyrene (OCS)	Produced as by-products during waste incineration and industrial processes involving carbon and chlorine (eg, during metal, solvent or pesticide manufacturing) PCBs: until 1970s widely used as insulating and cooling fluids	PCBs, dioxins, furans, PCN: interfere with steroid synthesis through aryl hydrocarbon receptor binding (CDC)[22 23] HCB: affects male and female fertility in animal studies[24] OCS: metabolites possibly interfere with thyroid homeostasis through binding with plasma proteins[25]
3. Pesticides	3.1 Organochlorines 3.2 Carbamates 3.3 Organophosphates 3.4 Tributyltin 3.5 Pyrethroids 3.6 Other pesticides	Used in agriculture Other purposes include wood preservation, anti-fouling, parasite treatment and public hygiene	Oestrogenic or anti-androgenic effects in vitro, reproductive toxicity in animal models, and subfertility or endocrine alterations in human studies[26 27]
4. Phthalates	4.1 Di-2-ethylhexyl phthalate (DEHP), di-isononyl phthalate (DNP), di-n-hexyl phthalate (DHP) 4.2 Benzyl butyl phthalate (BBP) 4.3 Dibutyl phthalate (DBP) 4.4 Diethyl phthalate (DEP)	Many industrial applications High molecular weight phthalates (DEHP, DNP, DHP) primarily used a plasticisers in polyvinyl chloride (PVC) Low molecular weight phthalates (BBP, DBP, DEP) used as solvents and plasticisers in cosmetics, adhesives, ink, dyes and plastic packaging	DEHP, DNP, DHP, BBP, DBP: affect the development of male reproductive organs in animal studies[28–32] DEP, DBP, BBP: possibly interfere with male reproductive hormone levels in children[33]
5. Organic solvents	5.1 Ethylene glycol ethers (EGEs) 5.2 Styrene 5.3 Toluene 5.4 Xylene 5.5 Trichloroethylene (TCE) 5.6 Perchloroethylene (PCE)	EGEs, toluene, xylene: widely used in, for example, paints, adhesives, thinners, lacquers and resins Styrene: used for producing polystyrene plastics and resins TCE, PCE: used for metal degreasing and other industrial cleaning purposes	EGEs: reproductive toxicity in animal studies and possibly reduced fertility and menstrual length variability in women[34] Styrene: styrene dimers and trimers bind to oestrogen receptors in vitro[35] Toluene, xylene, TCE: possibly interfere with reproductive hormone levels in humans[36–38] PCE: dry cleaning has been associated with menstrual disorders, infertility and delayed conception in women[34]
6. Bisphenol A	None	Used in the production of polycarbonate plastic and epoxy resins	Oestrogenic effects according to various in vitro and in vivo studies[39]
7. Alkylphenolic compounds	7.1 Alkylphenolic ethoxylates (APEs) 7.2 Alkylphenols (APs)	APEs: commonly used surfactants in, for example, detergents, pesticides and cosmetics APs: primarily used to produce APEs	APE metabolites, which include APs and short chain APEs, interact with oestrogen receptors in vitro[40]
8. Brominated flame retardants	8.1 Tetrabromobisphenol A (TBBPA) 8.2 Hexabromocyclodecane (HBCD) 8.3 Polybrominated disphenyl ethers (PBDEs)	Widely used in the polymer industry, for example in the production of PVC, epoxy resins, polyester and rubber	TBBPA, HBCD, PBDEs: interfere with thyroid hormone levels[41] TBBPA, PBDEs: possibly interfere with oestrogen metabolism through oestrogen sulfotransferase inhibition[41]
9. Metals	9.1 Arsenic 9.2 Cadmium 9.3 Copper 9.4 Lead 9.5 Mercury	Used in, for example, the electrical/electronics industry, for construction, in batteries, dyes, pesticides and dental amalgam, and as chemical intermediates	Arsenic: inhibits glucocorticoid gene transcription in vitro and thought to have similar effects on other steroid receptors[42] Cadmium, coppers, lead, mercury: testicular toxicity in animal models or altered hormone levels and/or male subfertility in humans[43]
10. Miscellaneous	10.1 Benzophenones 10.2 Parabens 10.3 Siloxanes	Benzophenones: UV screens used in cosmetics and the plastic industry Parabens: widely used preservatives in cosmetics and the pharmaceutical industry Siloxanes: intermediates in the polymer industry and ingredients in personal care products and precision cleaning agents	Benzophenones: bind with oestrogen receptors in vitro and exert oestrogenic effects in animal studies[44] Parabens: oestrogenic activity in vitro and in animal studies[45] Siloxanes: oestrogenic and anti-oestrogenic activity in animal studies[46]

Table 3 Definitions of exposure scores

0	Exposure is unlikely to occur (or does not exceed general population background levels)
1	Exposure is possible for some workers, but probability is low (involves less than 10% of workers with this job title)
2	Exposure is likely to occur (in more than 10% of workers with this job title)
9	Job title provides too little information to classify exposure

No distinction was made between the various routes of exposure (inhalation, ingestion or dermal).

The exposure probability scores were assigned by means of consensus discussions in which the original scores were taken into account where possible, but no prior individual assessments were performed. In preparation for the discussion meetings, the experts studied the reference material and reviewed the job descriptions. Furthermore, the expert panel's exposure estimates were based on their knowledge of tasks and working environments in various occupations in the UK during the relevant period. First, the complete list was screened to identify job titles that were highly unlikely to involve any exposure and job titles that were unclassifiable. The remaining occupations were scored for each of the 10 chemical groups and 33 subgroups, taking into account the original exposure scores where possible. The exposure probability scores for subgroups (eg, cadmium, arsenic, copper, lead and mercury) were summarised in the group score (metals), so that the group score equalled the highest exposure probability score in the subgroups. Likewise, the 10 group scores were summarised in the overall exposure probability score. During the consensus meeting, the reasons for the positive exposure scores (score 1 or 2) were documented and used to define 57 different exposure scenarios, such as "exposure to fumes from burning buildings", "exposure to refuse contaminated with PCBs", "exposure to indoor exhaust fumes", "working with spray paints" and "applying pesticides against insects and rodents".

After completing the expert assessments, 24 job titles which had not been identified as unexposed occupations in the first screening, were left as unexposed. These occupations were double checked, as well as the occupations that received an "unclassifiable" score. For each chemical group, both the group score and the subgroup scores were checked for consistency over all exposed job titles. We also ensured that job titles with a similar exposure scenario received the same exposure probability scores. The few inconsistencies that were detected were corrected in the final JEM.

RESULTS

The final structure of the JEM is illustrated in table 4. "Senior officials in national government" is an example of a job title for which exposure to any chemical group is classified as unlikely. For the second job title, "electricians, electrical fitters", exposure is classified as possible, because some workers may reach relevant exposure levels for lead during soldering. Glass and ceramics makers, decorators and finishers are classified as probably exposed to arsenic, cadmium and lead, because arsenic and lead are used for glass making, and cadmium and lead are constituents in glass and ceramics dyes. These workers are also possibly exposed to organic solvents from coatings. "Beauticians and related occupations" involves working with cosmetics, which are considered to be an exposure source for many chemicals, although the probability of exposure to organic solvents, alkylphenolic compounds, benzophenones and siloxanes is considered to be low. "Chemical and related process operatives" is an example of a job title that is too broad to classify the exposure probability.

Some examples of exposure scenarios are listed in table 5, which shows some scenarios and exposures that were considered for the glass and ceramics industry, for people working

Table 4 The job exposure matrix for five different job titles

Code	SOC2000 job title	Overall exposure score*	Chemical groups†	Group scores*	Chemical subgroups†	Subgroup scores*	Exposure scenarios
1111	Senior officials in national government	0	–	–	–	–	–
5241	Electricians, electrical fitters	1	Metals (9)	1	Lead (9.4)	1	Lead solder
5491	Glass and ceramics makers, decorators and finishers	2	Organic solvents (5)	1	EGEs (5.1)	1	Glass making chemicals; dyes for glass and ceramics; coatings
					Toluene (5.3)	1	
					Xylene (5.4)	1	
			Metals (9)	2	Arsenic (9.1)	2	
					Cadmium (9.2)	2	
					Lead (9.4)	2	
6222	Beauticians and related occupations	2	Phthalates (4)	2	DEHP, DNP, DHP (4.1)	1	Cosmetics
					BBP (4.2)	2	
					DBP (4.3)	2	
					DEP (4.4)	2	
			Organic solvents (5)	1	EGEs (5.1)	1	
			Alkylphenolic compounds (7)	1	APEs (7.1)	1	
					APs (7.2)	1	
			Miscellaneous (10)	2	Benzophenones (10.1)	1	
					Parabens (10.2)	2	
					Siloxanes (10.3)	1	
8114	Chemical and related process operatives	9	–	–	–	–	–

*Exposure scores refer to the exposure probabilities formulated in table 3. †Only chemical groups and subgroups to which exposure is possible (1) or probable (2) are shown. APs, alkylphenols; APEs, alkylphenolic ethoxylates; BBP, benzyl butyl phthalate; DBP, dibutyl phthalate; DEHP, di-2-ethylhexyl phthalate; DEP, diethyl phthalate; DHP, di-n-hexyl phthalate; DNP, di-isononyl phthalate; EGEs, ethylene glycol ethers; SOC2000, UK Standard Occupational Classification 2000.

Table 5 Exposure scenarios showing the reasons for assigning exposure probability scores in the job exposure matrix (JEM)

Exposure scenarios	JEM chemical groups involved	JEM chemical subgroups involved
Exposures during the manufacturing and processing of glass and ceramics		
Glass making chemicals	Metals (9)	Arsenic (9.1)
		Lead (9.4)
Dyes for glass and ceramics	Metals (9)	Cadmium (9.2)
		Lead (9.4)
Exposures during processing of metals and using metal end products		
Lead solder	Metals (9)	Lead (9.4)
Ammunition for firearms	Metals (9)	Lead (9.4)
Metal cleaning and degreasing agents	Organic solvents (5)	EGEs (5.1)
		TCE (5.5)
		PCE (5.6)
Exposure to pesticides		
Pesticides for general agricultural purposes	Pesticides (3)	Organochlorines (3.1)
		Carbamates (3.2)
		Organophosphates (3.3)
		Pyrethroids (3.5)
		Other pesticides (3.6)
	Phthalates (4)	DEHP, DNP, DHP (4.1)
		DBP (4.3)
		DEP (4.4)
	Organic solvents (5)	EGEs (5.1)
		Toluene (5.3)
		Xylene (5.4)
	Alkylphenolic compounds (7)	APEs (7.1)
		APs (7.2)
	Metals (9)	Copper (9.3)
Sheep dipping pesticides	Pesticides (3)	Organophosphates (3.3)
		Pyrethroids (3.5)
		Other pesticides (3.6)
	Phthalates (4)	DEHP, DNP, DHP (4.1)
		DBP (4.3)
		DEP (4.4)
	Organic solvents (5)	EGEs (5.1)
		Toluene (5.3)
		Xylene (5.4)
	Alkylphenolic compounds (7)	APEs (7.1)
		APs (7.2)

APs, alkylphenols; APEs, alkylphenolic ethoxylates; DBP, dibutyl phthalate; DEHP, di-2-ethylhexyl phthalate; DEP, diethyl phthalate; DHP, di-n-hexyl phthalate; DNP, di-isononyl phthalate; EGEs, ethylene glycol ethers; PCE, perchloroethylene; TCE, trichloroethylene.

with metals or metal end products, and for jobs in agricultural settings.

Of the 353 job titles, 237 (67%) were classified as not exposed to any chemical group and 13 (4%) were ''unclassifiable''. Of the remaining 103 job titles (29%), 60 (17%) were classified as possibly exposed and 43 (12%) as probably exposed to one or more chemical groups in the JEM. The unexposed job titles mostly concerned managers, professionals in science, technology, teaching, business and public services, administrative and secretarial occupations, and sales and customer service occupations. The exposed job titles were predominantly skilled trade occupations and process, plant and machine operatives.

Table 6 shows the frequencies of the exposure probability scores among the job titles in the JEM for each chemical group separately. Metals and organic solvents are most often linked to an occupation in the JEM. Regarding organic solvents, the positive exposure scores most often refer to ethylene glycol ethers (EGEs), toluene and xylene, although EGE exposure was not considered to be very likely in any occupation. Exposure to metals most often concerns copper or lead. Other frequently scored chemical groups include PAHs, pesticides, phthalates and alkylphenolic compounds, but the latter group only scored in the ''possible'' category. The remaining chemicals (polychlorinated organic compounds, bisphenol A, brominated flame retardants, benzophenones, parabens and siloxanes) involve very few occupations in the JEM.

The most commonly documented exposure scenarios were exposure to exhaust fumes (27 times), copper fumes (10 times) and lead fumes (seven times), and working with lead solder (five times), metal cleaning and degreasing agents (seven times), pesticides for general agricultural purposes (13 times), adhesives (nine times) and coatings (five times). The remaining exposure scenarios mostly applied to a single job title.

Differences between the exposures scores in the 2002 JEM (available for pesticides, dioxins, phthalates, bisphenol A, alkylphenolic compounds and metals) and the corresponding new exposure scores demonstrate some improvements in working environments. For example, 10 job titles that were considered exposed to polychlorinated compounds according to the 2002 JEM were not exposed in the new JEM. Many of these job titles involve handling electronic goods, which used to be a source of polychlorinated biphenyls (PCB) exposure but have not been so for the last 10 years. For four job titles, the original exposure probability scores for metals were adjusted because of reduced amounts of lead in paint and petrol. Three job titles that involved domestic cleaning were no longer considered to be exposed to alkylphenolic compounds. In nine other cases, exposure scores were adjusted because of disparities between the job descriptions and chemical groups used in the 2002 JEM and in the new JEM, and 12 job titles were now judged to be ''unclassifiable''. Additionally, several exposure scores were adjusted because the experts did not find them appropriate and the reasons for the original scores were unclear. The original JEM scores remained unaltered for 254 job titles.

DISCUSSION

Based on a JEM developed by van Tongeren *et al* in 2002, we constructed a new JEM for estimating occupational exposure to endocrine disruptors in epidemiological studies. In this JEM, 353 job titles were linked to exposure probability scores for 10 chemical groups and 33 chemical subgroups. We updated the original JEM by incorporating current knowledge on endocrine disrupting chemicals and by focusing the exposure estimates on the previous 10 years. Additionally, the reasons for the exposure probability scores were documented as 57 exposure scenarios to facilitate further adjustments. These changes are intended to increase the performance of the JEM and encourage its widespread use. Nevertheless, the JEM has some limitations which are discussed below.

We aimed to identify as many potential endocrine disruptors as possible from the literature. This resulted in a large selection of chemical groups and subgroups with varying levels of evidence for endocrine disrupting potential and with very diverse industrial purposes. It was difficult to classify exposure for some specific chemicals, especially if little background information was available. It might be possible to achieve more accurate exposure estimates by extending the literature search or by consulting other experts for additional information on occupations at risk. The exposure scenarios that describe the reasoning for the exposure scores are meant to be helpful for improving the JEM and for making adjustments to account for differences in exposure probabilities over time and between

Table 6 Prevalence of exposure scores among the 353 UK SOC2000 job titles in the job exposure matrix

Chemical group	No of job titles with score 1	No of job titles with score 2	No of job titles with score 1 or 2 (percentage of total)
1. Polycyclic aromatic hydrocarbons	27	5	32 (9.1%)
2. Polychlorinated organic compounds	3	1	4 (1.1%)
2.1 PCBs	1	1	2 (0.6%)
2.2 Dioxins, furans, PCN	3	1	4 (1.1%)
2.3 HCB	3	1	4 (1.1%)
2.4 OCS	3	1	4 (1.1%)
3. Pesticides	13	7	20 (5.7%)
3.1 Organochlorines	7	6	13 (3.7%)
3.2 Carbamates	12	7	19 (5.4%)
3.3 Organophosphates	9	7	16 (4.5%)
3.4 Tributyltin	0	0	0 (0.0%)
3.5 Pyrethroids	12	7	19 (5.4%)
3.6 Other pesticides	13	7	20 (5.7%)
4. Phthalates	16*	8	24 (6.8%)
4.1 DEHP, DNP, DHP	12	2	14 (4.0%)
4.2 BBP	9	8	17 (4.8%)
4.3 DBP	19	5	24 (6.8%)
4.4 DEP	9	5	14 (4.0%)
5. Organic solvents	33	13	46 (13.0%)
5.1 EGEs	32	0	32 (9.1%)
5.2 Styrene	2	0	2 (0.6%)
5.3 Toluene	12	18	30 (8.5%)
5.4 Xylene	23	7	30 (8.5%)
5.5 TCE	11	0	11 (3.1%)
5.6 PCE	10	1	11 (3.1%)
6. Bisphenol A	1	0	1 (0.3%)
7. Alkylphenolic compounds	19	0	19 (5.4%)
7.1 APEs	19	0	19 (5.4%)
7.2 APs	11	0	11 (3.1%)
8. Brominated flame retardants	4	0	4 (1.1%)
8.1 TBBPA	2	0	2 (0.6%)
8.2 HBCD	3	0	3 (0.9%)
8.3 PBDEs	4	0	4 (1.1%)
9. Metals	31	14	45 (15.3%)
9.1 Arsenic	6	2	8 (2.3%)
9.2 Cadmium	1	5	6 (1.7%)
9.3 Copper	21	7	28 (7.9%)
9.4 Lead	21	6	27 (7.7%)
9.5 Mercury	1	3	4 (1.1%)
10. Miscellaneous	2*	3	5 (1.4%)
10.1 Benzophenones	4	0	4 (1.1%)
10.2 Parabens	0	3	3 (0.9%)
10.3 Siloxanes	5	0	5 (1.4%)

*Exposure probability scores for the chemical groups correspond with the highest score of the chemical subgroups. Therefore, frequencies of subgroup scores can exceed the frequency of corresponding group scores.

APs, alkylphenols; APEs, alkylphenolic ethoxylates; BBP, benzyl butyl phthalate; DBP, dibutyl phthalate; DEHP, di-2-ethylhexyl phthalate; DEP, diethyl phthalate; DHP, di-n-hexyl phthalate; DNP, di-isononyl phthalate; EGEs, ethylene glycol ethers; HBCD, hexabromocyclodecane; HCB, hexachlorobenzene; OCS, octachlorostyrene; PBDEs, polybrominated disphenyl ethers; PCBs, polychlorinated biphenyls; PCE, perchloroethylene; PCN, dioxins, furans, polychlorinated naphthalene; SOC2000, UK Standard Occupational Classification 2000; TBBPA, tetrabromobisphenol A; TCE, trichloroethylene.

countries. For example, in applying the JEM to our Dutch case–referent study on hypospadias and cryptorchidism we adjusted the exposure probability scores for the scenario ''working with sheep dipping pesticides'', as sheep dipping is much less common in The Netherlands than in the UK. We also considered ''exposure to lead fumes'' by pipe fitters and plumbers to be less likely than in the UK. New regulations on, for example, the uses of organic solvents, metals and alkylphenolic compounds, may require specific adjustments to the JEM for younger subjects. In general, we recommend other researchers not to use the JEM ''blindly'', but to first consider the generalisibility of the exposure probability scores to their specific study population.

The vast majority of the job titles in the JEM were classified as unexposed. Most of these were easily recognised by managerial and administrative job descriptions. For applying the JEM, this has the practical advantage that an efficient coding strategy can be used in which unexposed occupations are coded with less detail. However, the restricted number of exposed occupations also means that, depending on the distribution of job titles within a specific study population, studying associations between endocrine disruptor exposure and adverse health effects at the chemical group or subgroup level may require a very large sample size.

The cells of our matrix represent exposure probabilities, which are only a crude measure of exposure. We considered the possibility of assessing the level of exposure as well, but concluded that we had too little information to produce such estimates. In some cases, however, the exposure scenarios can be used as an indication of the level of exposure. For example, the scenario ''working with tar'' can be expected to involve higher levels of PAHs compared to the scenario ''exposure to environmental tobacco smoke''. Taking into account the exposure scenarios may therefore provide more insight into the association between specific chemical groups and subgroups and the outcome of interest.

As stated earlier, a major drawback of all JEMs is that they do not account for variability in tasks and working environments within job titles. This could result in substantial misclassification, especially when a JEM is based on a broad occupational classification system developed for socio-economic purposes rather than exposure assessment, which is often the case. Strategies to refine JEM exposure estimates have been described by Semple *et al* and Kennedy *et al* for exposure assessment in studies on risk factors for Parkinson's disease and asthma.[16 17] In both studies, a method was developed in which JEM exposure estimates were modified based on task specific

Main messages

- Occupationally encountered endocrine disruptors include a wide variety of industrial chemicals and by-products, such as polycyclic aromatic hydrocarbons, dioxins, pesticides, phthalates, organic solvents, brominated flame retardants and metals.
- A new up-to-date and comprehensive job exposure matrix for potential endocrine disruptors was developed for use in exposure assessment in epidemiological research.

Policy implication

The job exposure matrix described here could be a valuable tool for exposure assessment in studies on the health risks posed by the increasing number of endocrine disruptors.

information from interviews. With respect to the asthma JEM, this method resulted in stronger associations between risk factors and asthma, indicating a reduction in non-differential misclassification.[16]

In the current JEM, the documented exposure scenarios describing the reasons for the exposure probability scores also allow further refinements. Task specific information from questionnaires, interviews or diaries can be used to verify the exposure scenarios for the subjects in a study population. For example, according to the JEM, all workers with the job title ''farmer'' are probably exposed to pesticides. However, from the task descriptions, it may become clear that some subjects with this job title have certain odd jobs around a farm (eg, feeding farm animals) where pesticide exposure is less likely. Especially with such exercises, we believe that the JEM can be a valuable tool for exposure assessment in community based studies on the health risks of the increasing number of endocrine disruptors.

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Copies of the JEM and accompanying background information are available as an SPSS database and Excel spreadsheet from the corresponding author.

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REFERENCES

1. **Damstra T,** Barlow S, Bergman A, *et al*. *Global assessment of the state-of-the-science of endocrine disruptors*. Geneva: World Health Organization, 2002.
2. **Skakkebaek NE,** Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *Hum Reprod* 2001;**16**:972–8.
3. **Heilier JF,** Nackers F, Verougstraete V, *et al*. Increased dioxin-like compounds in the serum of women with peritoneal endometriosis and deep endometriotic (adenomyotic) nodules. *Fertil Steril* 2005;**84**:305–12.
4. **Darbre PD.** Environmental oestrogens, cosmetics and breast cancer. *Best Pract Res Clin Endocrinol Metab* 2006;**20**:121–43.
5. **Hess-Wilson JK,** Knudsen KE. Endocrine disrupting compounds and prostate cancer. *Cancer Lett* 2006;**241**:1–12.
6. **Safe SH.** Endocrine disruptors and human health—is there a problem? An update. *Environ Health Perspect* 2000;**108**:487–93.
7. **Joffe M.** Are problems with male reproductive health caused by endocrine disruption? *Occup Environ Med* 2001;**58**:281–7.
8. **Safe S.** Clinical correlates of environmental endocrine disruptors. *Trends Endocrinol Metab* 2005;**16**:139–44.
9. **van Tongeren M,** Nieuwenhuijsen MJ, Gardiner K, *et al*. A job-exposure matrix for potential endocrine-disrupting chemicals developed for a study into the association between maternal occupational exposure and hypospadias. *Ann Occup Hyg* 2002;**46**:465–77.
10. **Vrijheid M,** Armstrong B, Dolk H, *et al*. Risk of hypospadias in relation to maternal occupational exposure to potential endocrine disrupting chemicals. *Occup Environ Med* 2003;**60**:543–50.
11. **Pierik FH,** Burdorf A, Deddens JA, *et al*. Maternal and paternal risk factors for cryptorchidism and hypospadias: a case-control study in newborn boys. *Environ Health Perspect* 2004;**112**:1570–6.
12. **Teschke K,** Olshan AF, Daniels JL, *et al*. Occupational exposure assessment in case-control studies: opportunities for improvement. *Occup Environ Med* 2002;**59**:575–93.
13. **Tielemans E,** Heederik D, Burdorf A, *et al*. Assessment of occupational exposures in a general population: comparison of different methods. *Occup Environ Med* 1999;**56**:145–51.
14. **Dosemeci M,** Cocco P, Gomez M, *et al*. Effects of three features of a job-exposure matrix on risk estimates. *Epidemiology* 1994;**5**:124–7.
15. **Kauppinen T,** Toikkanen J, Pukkala E. From cross-tabulations to multipurpose exposure information systems: a new job-exposure matrix. *Am J Ind Med* 1998;**33**:409–17.
16. **Kennedy SM,** Le MN, Choudat D, *et al*. Development of an asthma specific job exposure matrix and its application in the epidemiological study of genetics and environment in asthma (EGEA). *Occup Environ Med* 2000;**57**:635–41.
17. **Semple SE,** Dick F, Cherrie JW. Exposure assessment for a population-based case-control study combining a job-exposure matrix with interview data. *Scand J Work Environ Health* 2004;**30**:241–8.
18. **Office for National Statistics**. *Standard occupational classification 2000. Volume 1: Structure and descriptions of unit groups*. London: Stationery Office, 2000.
19. **Institute for Environment and Health**. *Chemicals purported to be endocrine disruptors: a compilation of published lists (web report W20)*. Leicester: Medical Research Council, 2005.
20. **Colborn T,** Dumanoski D, Myers JP. *Widespread pollutants with endocrine-disrupting effects: chemicals implicated*. Available at http://www.ourstolenfuture.org/basics/chemlist.htm (accessed 28 April 2009).
21. **Arcaro KF,** O'Keefe PW, Yang Y, *et al*. Antiestrogenicity of environmental polycyclic aromatic hydrocarbons in human breast cancer cells. *Toxicology* 1999;**133**:115–27.
22. **Centers for Disease Control and Prevention**. *Third national report on human exposure to environmental chemicals*. National Center for Environmental Health, publication no. NCEH05-0570. Atlanta, GA: CDC, 2005.
23. **Omura M,** Masuda Y, Hirata M, *et al*. Onset of spermatogenesis is accelerated by gestational administration of 1,2,3,4,6,7-hexachlorinated naphthalene in male rat offspring. *Environ Health Perspect* 2000;**108**:539–44.
24. **Agency for Toxic Substances and Disease Registry**. *Toxicological profile for hexachlorobenzene*. Atlanta, GA: ATSDR, 2002.
25. **Sandau C,** Meerts I, Letcher R, *et al*. Identification of 4-hydroxyheptachlorostyrene in polar bear plasma and its binding activity to transthyretin: a metabolite of octachlorostyrene? *Environ Sci Technol* 2000;**34**:3871–7.
26. **Bretveld R,** Brouwers M, Ebisch I, *et al*. Influence of pesticides on male fertility. *Scand J Work Environ Health* 2007;**33**:13–28.
27. **Bretveld RW,** Thomas CM, Scheepers PT, *et al*. Pesticide exposure: the hormonal function of the female reproductive system disrupted? *Reprod Biol Endocrinol* 2006;**4**:30.
28. **Center for the Evaluation of Risks to Human Reproduction**. *Expert panel report on di(2-ethylhexyl)phthalate*. US Department of Health and Human Services, publication no. NTP-CERHR-CEHP-00. Research Triangle Park, NC: CERHR, 2000.
29. **Center for the Evaluation of Risks to Human Reproduction**. *Expert panel report on di-isononyl phthalate*. US Department of Health and Human Services, publication no. NTP- CERHR-DINP-00. Research Triangle Park, NC: CERHR, 2000.
30. **Center for the Evaluation of Risks to Human Reproduction**. *Expert panel report on di-n-hexyl phthalate*. US Department of Health and Human Services, publication no. NTP- CERHR-DNHP-00. Research Triangle Park, NC: CERHR, 2000.
31. **Center for the Evaluation of Risks to Human Reproduction**. *Expert panel report on butyl benzyl phthalate*. US Department of Health and Human Services, publication no. NTP- CERHR-BBP-00. Research Triangle Park, NC: CERHR, 2000.
32. **National Center for the Evaluation of Risks to Human Reproduction**. *Expert panel report on di-n-butyl phthalate*. US Department of Health and Human Services, publication no. NTP-CERHR-DBP-00. Research Triangle Park, NC: CERHR, 2000.
33. **Main KM,** Mortensen GK, Kaleva MM, *et al*. Human breast milk contamination with phthalates and alterations of endogenous reproductive hormones in infants three months of age. *Environ Health Perspect* 2006;**114**:270–6.
34. **Lindbohm ML.** Effects of occupational solvent exposure on fertility. *Scand J Work Environ Health* 1999;**25**(Suppl 1):44–6.
35. **Ohyama KI,** Nagai F, Tsuchiya Y. Certain styrene oligomers have proliferative activity on MCF-7 human breast tumor cells and binding affinity for human estrogen receptor. *Environ Health Perspect* 2001;**109**:699–703.
36. **Chia SE,** Goh VH, Ong CN. Endocrine profiles of male workers with exposure to trichloroethylene. *Am J Ind Med* 1997;**32**:217–22.
37. **Reutman SR,** LeMasters GK, Knecht EA, *et al*. Evidence of reproductive endocrine effects in women with occupational fuel and solvent exposures. *Environ Health Perspect* 2002;**110**:805–11.
38. **Luderer U,** Bushley A, Stover BD, *et al*. Effects of occupational solvent exposure on reproductive hormone concentrations and fecundability in men. *Am J Ind Med* 2004;**46**:614–26.
39. **Maffini MV,** Rubin BS, Sonnenschein C, *et al*. Endocrine disruptors and reproductive health: the case of bisphenol-A. *Mol Cell Endocrinol* 2006;**254-255**:179–86.
40. **White R,** Jobling S, Hoare SA, *et al*. Environmentally persistent alkylphenolic compounds are estrogenic. *Endocrinology* 1994;**135**:175–82.
41. **Birnbaum LS,** Staskal DF. Brominated flame retardants: cause for concern? *Environ Health Perspect* 2004;**112**:9–17.
42. **Kaltreider RC,** Davis AM, Lariviere JP, *et al*. Arsenic alters the function of the glucocorticoid receptor as a transcription factor. *Environ Health Perspect* 2001;**109**:245–51.
43. **Queiroz EK,** Waissmann W. Occupational exposure and effects on the male reproductive system. *Cad Saude Publica* 2006;**22**:485–93.
44. **Seidlova-Wuttke D,** Jarry H, Wuttke W. Pure estrogenic effect of benzophenone-2 (BP2) but not of bisphenol A (BPA) and dibutylphtalate (DBP) in uterus, vagina and bone. *Toxicology* 2004;**205**:103–12.
45. **Golden R,** Gandy J, Vollmer G. A review of the endocrine activity of parabens and implications for potential risks to human health. *Crit Rev Toxicol* 2005;**35**:435–58.
46. **McKim JM Jr,** Wilga PC, Breslin WJ, *et al*. Potential estrogenic and antiestrogenic activity of the cyclic siloxane octamethylcyclotetrasiloxane (D4) and the linear siloxane hexamethyldisiloxane (HMDS) in immature rats using the uterotrophic assay. *Toxicol Sci* 2001;**63**:37–46.
47. **Agency for Toxic Substances and Disease Registry**. *Toxicological profiles*. Available from http://www.atsdr.cdc.gov (accessed 29 April 2009).
48. **European Chemicals Bureau**. *Risk assessment report on existing chemicals*. Joint Research Centre of the European Commission. Available from http://ecb.jrc.ec.europa.eu/documentation/ (accessed 29 April 2009).

49. **UK Government**. *Voluntary agreement. Risk reduction for nonylphenol, nonylphenol ethoxylates, octylphenol and octylphenol ethoxylates by chemical supply industry & downstream users*. April 2004. Available from http://www.defra.gov.uk/ENVIRONMENT/chemicals/phenols-va/voluntary-ag.pdf (accessed 29 April 2009).
50. **Health and Safety Executive**. *Pesticide register of UK approved products*. Available from https://secure.pesticides.gov.uk/pestreg/ (accessed 29 April 2009).
51. **Health and Safety Executive**. *Biocides and pesticides*. See http://www.hse.gov.uk/biocides (accessed 29 April 2009).

Occupational exposure to potential endocrine disruptors: further development of a job exposure matrix

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