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Sex and Gender Analysis of Toxicity and Epidemiology Data on Environmental Chemicals in the Three Major Toxicology Databases

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Abstract

Background: As sex and gender are important considerations in the assessment of toxic chemicals, we investigated whether sex and gender issues have been adequately considered in toxicological databases.
Materials and Methods: A systemic review was conducted on the toxicity and epidemiology data of eight environmental chemicals (*i.e.*, cadmium [Cd], lead [Pb], benzene, toluene, formaldehyde, and tetrachloroethylene [TCE], bis(2-ethylhexyl) phthalate [DEHP], and bisphenol A [BPA]) that appear in three toxicological databases (*i.e.*, Hazardous Substances Data Bank, Integrated Risk Information System, and the European Chemicals Agency databases).
Results: Systemic reviews on 4160 data entries pertaining to eight chemicals in three databases revealed that only 13.5% of these were sourced from male and female combined (MF) studies, whereas, 40.6% of the total number of examined entries was sourced from the study in which the sex of the subject was not mentioned.
Conclusions: To accurately evaluate the hazardous effect of chemicals, toxicity tests should be designed and conducted for both sexes, and the corresponding endpoints should cover gender concerns. Therefore, databases listing toxicity data as part of the open source literature should select information from MF toxicity and epidemiology studies.

Keywords: environmental chemicals, toxicological databases, sex- and gender-biased toxicity data

Introduction

The ubiquitous use of chemicals in our daily life has resulted in significant conveniences in our daily lives. However, it has also caused some adverse impacts to human health and the environment. We are witnessing a rise in the incidence of a number of diseases, which is suspected as being significantly contributed to by environmental chemicals.[1,2] A growing body of scientific evidence indicates that exposure to environmental chemicals may contribute to the development and exacerbation of human diseases. Risk assessment is a useful tool to minimize adverse impacts while maximizing the benefits of chemical use. Risk assessment entails three analytic steps (*i.e.*, hazard identification, dose–response assessment, and exposure assessment) followed by a fourth step (risk characterization). The results of the first three steps are integrated to yield information on the probability that the adverse effects described in the hazard identification will occur under the conditions outlined in the exposure assessment.[3] This process provides a scientific basis for risk management decisions, such as, developing regulations pertaining to chemicals.

A number of recent studies indicate that exposures to chemicals affect different bodies in varied ways, as peoples' lives and health are influenced by both biological (sex-related) and social (gender-related) factors.[4] Not only do women and men possess different vulnerabilities to exposure based on biology, they also face disparate health risks based on gendered practices, as well as socioeconomic and cultural circumstances. Sex and gender are important considerations in the assessment and regulation of toxic chemicals, as male and female bodies respond to harmful chemicals in different ways, and men and women tend to have distinct patterns of use and exposure to chemicals based on their particular social locations.[5,6]

Ensuring public health and safety with regard to chemical use in general and sex- and gender-related issues in particular requires a formal risk assessment process. The toxic potential

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of chemicals is evaluated in the first two steps of risk assessment (*i.e.*, hazard identification and dose–response assessment), and most often, toxicity data from a toxicity database are used for such identification and evaluation. In this context, to investigate whether sex and gender issues have been adequately considered in toxicological databases that are used in the risk assessment process, we conducted a systemic review on the toxicity data of eight environmental chemicals that appear in three toxicological databases.

Materials and Methods

Eight organic and inorganic chemicals that are most commonly used and found in the environment were selected for the gender analysis. These chemicals are classified as follows: heavy metals (*i.e.*, cadmium [Cd] and lead [Pb]), volatile organic compounds (VOCs) (*i.e.*, benzene, toluene, formaldehyde, and tetrachloroethylene [PCE]), and endocrine-disrupting chemicals (EDCs) (*i.e.*, bis(2-ethylhexyl) phthalate [DEHP] and bisphenol A [BPA]). A brief description of each chemical is summarized in Supplementary Table S1. A systemic review was conducted on the toxicity data of these environmental chemicals, each of which appear in the National Institute of Health's (NIH's) Hazardous Substances Data Bank (HSDB), the U.S. Environmental Protection Agency's (USEPA's) Integrated Risk Information System (IRIS), and the European Chemicals Agency (ECHA) databases.

HSDB (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB),[7] a database managed by the NIH, focuses on the

Table 1. Systemic Reviews of Metal Toxicity Data Using Information Provided in the Three Databases

	Category	*Epidemiology*	In vivo	In vitro	*Total*
Cadmium					
HSDB	M	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	F	0 (0.0)	1 (16.7)	0 (0.0)	1 (10.0)
	MF	2 (66.7)	1 (16.7)	0 (0.0)	3 (30.0)
	NM	1 (33.2)	4 (66.7)	1 (100.0)	6 (60.0)
	Total	3	6	1	10
IRIS	M	15 (33.3)	6 (15.4)	0 (0.0)	21 (24.7)
	F	1 (2.2)	8 (20.5)	0 (0.0)	9 (10.6)
	MF	9 (20.0)	12 (30.8)	0 (0.0)	21 (24.7)
	NM	20 (44.4)	13 (33.3)	1 (100.0)	34 (40)
	Total	45	39	1	85
ECHA	M	7 (17.1)	25 (46.3)	0 (0.0)	32 (32.0)
	F	9 (22.0)	12 (22.2)	3 (60.0)	24 (24.0)
	MF	19 (46.3)	10 (18.5)	0 (0.0)	29 (29.0)
	NM	6 (14.6)	7 (13.0)	2 (40.0)	15 (15.0)
	Total	41	54	5	100
Total	M	22 (24.7)	31 (31.3)	0 (0.0)	53 (27.2)
	F	10 (11.2)	21 (21.2)	3 (42.9)	34 (17.4)
	MF	29 (32.6)	23 (23.2)	0 (0.0)	52 (26.7)
	NM	28 (31.5)	24 (24.2)	4 (57.1)	56 (28.7)
	Total	89	99	7	195
Lead					
HSDB	M	4 (7.7)	0 (0.0)	0 (0.0)	4 (6.7)
	F	3 (5.8)	2 (28.6)	0 (0.0)	5 (8.3)
	MF	7 (13.5)	2 (28.6)	0 (0.0)	9 (15.0)
	NM	38 (73.1)	3 (42.9)	1 (100.0)	42 (70.0)
	Total	52	7	1	60
IRIS	M				
	F				
	MF				
	NM				
	Total				
ECHA	M	44 (23.8)	0 (0.0)		44 (22.3)
	F	12 (6.5)	0 (0.0)		12 (6.1)
	MF	77 (41.6)	12 (100.0)		89 (45.2)
	NM	52 (28.1)	0 (0.0)		52 (26.4)
	Total	185	12		197
Total	M	48 (20.3)	0 (0.0)	0 (0.0)	48 (18.7)
	F	15 (6.3)	2 (10.5)	0 (0.0)	17 (6.6)
	MF	84 (35.4)	14 (73.7)	0 (0.0)	98 (38.1)
	NM	90 (38.0)	3 (15.8)	1 (100.0)	94 (36.6)
	Total	237	19	1	257

Values are total entries of data. Values in parenthesis are percentage of each entry data.

ECHA, European Chemicals Agency; F, Female-only study; HSDB, Hazardous Substances Data Bank; IRIS, Integrated Risk Information System; M, Male-only study; MF, Male and Female combined study; NM, study in which the sex of the subject was Not Mentioned.

Table 2. Systemic Reviews of Volatile Organic Compounds' Toxicity Data Using Information Provided in the Three Databases

	Category	*Epidemiology*	In vivo	In vitro	*Total*
Benzene					
HSDB	M	13 (40.6)	6 (15.4)	1 (14.3)	20 (25.6)
	F	0 (0.0)	6 (15.4)	0 (0.0)	6 (7.7)
	MF	1 (3.1)	7 (17.9)	0 (0.0)	8 (10.3)
	NM	18 (56.3)	20 (51.3)	6 (85.7)	44 (56.4)
	Total	32	39	7	78
IRIS	M	3 (8.3)	22 (31.0)	12 (15.8)	37 (20.2)
	F	11 (30.6)	15 (21.1)	3 (3.9)	29 (15.8)
	MF	2 (5.6)	15 (21.1)	4 (5.3)	21 (11.5)
	NM	20 (55.6)	19 (26.8)	57 (75.0)	96 (52.5)
	Total	36	71	76	183
ECHA	M	4 (16.7)	2 (20.0)		6 (17.6)
	F	0 (0.0)	1 (10.0)		1 (2.9)
	MF	12 (50.0)	1 (10.0)		13 (38.2)
	NM	8 (33.3)	6 (60.0)		14 (41.2)
	Total	24	10		34
Total	M	20 (21.7)	30 (25.0)	13 (15.7)	63 (21.4)
	F	11 (12.0)	22 (18.3)	3 (3.6)	36 (12.2)
	MF	15 (16.3)	23 (19.2)	4 (4.8)	42 (14.2)
	NM	46 (50.0)	45 (37.5)	63 (75.9)	154 (52.2)
	Total	92	120	83	295
Toluene					
HSDB	M	6 (18.2)	3 (8.8)	1 (100.0)	10 (14.7)
	F	6 (18.2)	0 (0.0)	0 (0.0)	6 (8.8)
	MF	1 (3.0)	0 (0.0)	0 (0.0)	1 (1.5)
	NM	20 (60.6)	31 (91.2)	0 (0.0)	51 (75.0)
	Total	33	34	1	68
IRIS	M	11 (19.0)	6 (18.2)		17 (18.7)
	F	2 (3.4)	7 (21.2)		9 (9.9)
	MF	9 (15.5)	8 (24.2)		17 (18.7)
	NM	36 (62.1)	12 (36.4)		48 (52.7)
	Total	58	33		91
ECHA	M	1 (20.0)	5 (8.8)	0 (0.0)	6 (7.9)
	F	0 (0.0)	9 (15.8)	3 (21.4)	12 (15.8)
	MF	0 (0.0)	20 (35.1)	0 (0.0)	20 (26.3)
	NM	4 (80.0)	23 (40.4)	11 (78.6)	38 (50.0)
	Total	5	57	14	76
Total	M	18 (18.8)	14 (11.3)	1 (6.7)	33 (14.0)
	F	8 (8.3)	16 (12.9)	3 (20.0)	27 (11.5)
	MF	10 (10.4)	28 (22.6)	0 (0.0)	38 (16.2)
	NM	60 (62.5)	66 (53.2)	11 (73.0)	137 (58.3)
	Total	96	124	15	235
Formaldehyde					
HSDB	M	10 (24.4)	14 (17.1)	0 (0.0)	24 (17.8)
	F	1 (2.4)	6 (7.3)	0 (0.0)	7 (5.2)
	MF	3 (7.3)	6 (7.3)	1 (8.3)	10 (7.4)
	NM	27 (65.9)	56 (68.3)	11 (91.7)	94 (69.6)
	Total	41	82	12	135
IRIS	M	0 (0.0)	3 (18.8)	0 (0.0)	3 (13.0)
	F	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	MF	0 (0.0)	8 (50.0)	0 (0.0)	8 (34.8)
	NM	3 (100.0)	5 (31.3)	4 (100.0)	12 (52.2)
	Total	3	16	4	23
ECHA	M	4 (7.3)	65 (48.5)	12 (22.2)	81 (33.3)
	F	1 (1.8)	5 (3.7)	1 (1.9)	7 (2.9)
	MF	10 (18.2)	28 (20.9)	1 (1.9)	39 (16)
	NM	40 (72.7)	36 (26.9)	40 (74.1)	116 (47.7)
	Total	55	134	54	243
Total	M	14 (14.1)	82 (35.3)	12 (17.1)	108 (26.9)
	F	2 (2.0)	11 (4.7)	1 (1.4)	14 (3.5)
	MF	13 (13.1)	42 (18.5)	2 (2.9)	57 (14.2)
	NM	70 (70.7)	95 (40.9)	55 (78.6)	222 (55.4)
	Total	99 (100)	232	70	401

(*continued*)

Table 2. (Continued)

	Category	*Epidemiology*	In vivo	In vitro	*Total*
Tetrachloroethylene					
HSDB	M	11 (20.0)	4 (5.3)	0 (0.0)	15 (11.5)
	F	3 (5.5)	7 (9.3)	0 (0.0)	10 (7.6)
	MF	12 (21.8)	20 (26.7)	0 (0.0)	32 (24.4)
	NM	29 (52.7)	44 (58.7)	1 (100.0)	74 (56.5)
	Total	55	75	1	131
IRIS	M	8 (11.3)	16 (27.1)	0 (0.0)	24 (16.8)
	F	27 (38.0)	10 (16.9)	0 (0.0)	37 (25.9)
	MF	8 (11.3)	6 (10.2)	0 (0.0)	14 (9.8)
	NM	28 (39.4)	27 (45.8)	13 (100.0)	68 (47.6)
	Total	71	59	13	143
ECHA	M	0 (0.0)	1 (12.5)		1 (11.1)
	F	0 (0.0)	0 (0.0)		0 (0.0)
	MF	0 (0.0)	5 (62.5)		5 (55.6)
	NM	1 (100.0)	2 (25.0)		3 (33.3)
	Total	1	8		9
Total	M	19 (15.0)	21 (14.8)	0 (0.0)	40 (14.1)
	F	30 (23.6)	17 (12.0)	0 (0.0)	47 (16.6)
	MF	20 (15.7)	31 (21.8)	0 (0.0)	51 (18.0)
	NM	58 (45.7)	73 (51.4)	14 (100.0)	145 (51.2)
	Total	127	142	14	283

Values are total entries of data. Values in parenthesis are percentage of each entry data.

toxicology of potentially hazardous chemicals. It provides information on human exposure, industrial hygiene, emergency handling procedures, environmental fate, regulatory requirements, nanomaterials, and related areas. The information in HSDB is assessed by a Scientific Review Panel. The IRIS (https://www.epa.gov/iris)[8] is the USEPA's toxicological database for human health and is located within the USEPA's National Center for Environmental Assessment.

An IRIS assessment includes the first two steps of the risk assessment process: hazard identification and dose–response assessment. IRIS is the preferred source of toxicity information for United States and international health organizations.

The ECHA (https://echa.europa.eu/information-on-chemicals)[9] is the major regulatory driver for implementing the EU's groundbreaking chemicals' legislation for the benefit of human health and the environment, as well as for innovation and competitiveness. ECHA provides details on the chemicals manufactured and imported in Europe, covering their hazardous properties, classification and labeling, and information on how to use them safely.

All the data were classified as belonging to one of the following categories: *in vitro*, *in vivo*, and epidemiology. Subsequently, sex and gender issues were analyzed for each category. Sex- and gender-analyzed toxicity data were classified as one of the following: Male-only study (M), Female-only study (F), Male and Female combined study (MF), or study in which the sex of the subject was Not Mentioned (NM). For each chemical and each database, the percentage of each category (M, F, MF, and NM) was calculated based on the amount of analyzed data.

Results

Systemic reviews of toxicity data of eight selected environmental chemicals were conducted using the information provided in the three databases (Table 1–4 and Supplementary Table S2). Reviews on metal toxicity data are presented in Table 1. In total, 195 entries on toxicity data were found in the three databases for Cd, and only 26.7% of these entries were sourced from studies using male as well as female subjects (MF studies). The percentages of data referring to combined (MF) studies in the epidemiology, *in vivo*, and *in vitro* categories were 32.6%, 23.2%, and 0%, respectively. For Pb, 38.1% of 257 data entries referred to MF studies (35.4%, 73.7%, and 0% for epidemiology, *in vivo*, *in vitro* studies, respectively).

Systemic reviews of VOC toxicity were conducted using the data from the three databases (Table 2). A total of 295 toxicity data entries were found for benzene, and only 14.2% of these data were sourced from studies using both male and female subjects. The percentages of data referring to combined (MF) studies in the epidemiology, *in vivo*, and *in vitro* categories were 16.3%, 19.2%, and 4.8%, respectively. For toluene, 16.2% of the total of 235 data entries was classified as belonging to the MF study subcategory (10.4%, 22.6%, and 0% of epidemiology, *in vivo* and *in vitro* studies, respectively). For formaldehyde, 14.2% of the total of 401 data entries was sourced from MF studies (13.1%, 18.5%, and 2.9% of epidemiology, *in vivo*, and *in vitro* studies, respectively). For PCE, 18.0% of the total of 283 data entries were sourced from MF studies (15.7%, 21.8%, and 0% of epidemiology, *in vivo* and *in vitro* studies, respectively).

Systemic reviews of EDC toxicity were conducted using the relevant data from the three databases (Table 3). For

Table 3. Systemic Reviews of Endocrine-Disrupting Chemical Toxicity Data Using Information Provided in the Three Databases

	Category	*Epidemiology*	In vivo	In vitro	*Total*
Bis(2-ethylhexyl) phthalate					
HSDB	M	7 (26.9)	47 (33.1)	1 (50.0)	55 (32.4)
	F	4 (15.4)	28 (19.7)	0 (0.0)	32 (18.8)
	MF	1 (3.8)	23 (16.2)	0 (0.0)	24 (14.1)
	NM	14 (53.8)	44 (31.0)	1 (50.0)	59 (34.7)
	Total	26	142	2	170
IRIS	M	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	F	0 (0.0)	0 (0.0)	1 (25.0)	1 (8.3)
	MF	0 (0.0)	6 (85.7)	0 (0.0)	6 (50.0)
	NM	1 (100.0)	1 (14.3)	3 (75.0)	5 (41.7)
	Total	1	7	4	12
ECHA	M	11 (10.9)	198 (44.1)	19 (15.3)	228 (33.8)
	F	17 (16.8)	55 (12.2)	8 (6.5)	80 (11.9)
	MF	16 (15.8)	94 (20.9)	1 (0.8)	111 (16.5)
	NM	57 (56.4)	102 (22.7)	96 (77.4)	255 (37.8)
	Total	101	449	124	674
Total	M	18 (14.1)	245 (41.0)	20 (15.4)	283 (33.1)
	F	21 (16.4)	83 (13.9)	9 (6.9)	113 (13.2)
	MF	17 (13.3)	123 (20.6)	1 (0.8)	141 (16.5)
	NM	72 (56.3)	147 (24.6)	100 (76.9)	319 (37.3)
	Total	128	598	130	856
Bisphenol A					
HSDB	M	3 (9.7)	4 (5.9)	0 (0.0)	7 (6.8)
	F	9 (29.0)	20 (29.4)	1 (25.0)	30 (29.1)
	MF	4 (12.9)	11 (16.2)	0 (0.0)	15 (14.6)
	NM	15 (48.4)	33 (48.5)	3 (75.0)	51 (49.5)
	Total	31	68	4	103
IRIS	M		0 (0.0)		0 (0.0)
	F		0 (0.0)		0 (0.0)
	MF		2 (28.6)		2 (28.6)
	NM		5 (71.4)		5 (71.4)
	Total		7		7
ECHA	M	7 (6.0)	216 (19.1)	23 (8.2)	246 (16.1)
	F	15 (12.9)	638 (56.4)	58 (20.6)	711 (46.5)
	MF	8 (6.9)	57 (5.0)	1 (0.4)	66 (4.3)
	NM	86 (74.1)	220 (19.5)	199 (70.8)	505 (33.0)
	Total	116	1131	281	1528
Total	M	10 (6.8)	216 (19.1)	23 (8.1)	253 (15.4)
	F	24 (16.3)	638 (56.4)	59 (20.7)	741 (45.2)
	MF	12 (8.2)	70 (5.8)	1 (0.4)	83 (5.1)
	NM	101 (68.7)	258 (21.4)	202 (70.9)	561 (34.2)
	Total	147	1206	285	1638

Values are total entries of data. Values in parenthesis are percentage of each entry data.

DEHP, a total 856 toxicity data entries were found in the three databases, with only 16.5% of the data having been sourced from MF studies. The percentages of data from MF studies were 13.3%, 20.6%, and 0.8% of epidemiology, *in vivo*, and *in vitro* studies, respectively. For BPA, only 5.1% of the total number of data entries (1638) was categorized as belonging to MF studies (8.2%, 5.8%, and 0.4% of epidemiology, *in vivo*, and *in vitro* studies, respectively).

In total, systemic reviews on 4160 data entries pertaining to eight chemicals in three databases (Table 4) revealed that only 13.5% of these were sourced from MF studies (4160 studies; 19.8%, 13.9%, and 1.3% of entries in epidemiology, *in vivo*, and *in vitro* categories, respectively). It was also confirmed that animal studies contribute important toxicological information, as number of entries for the epidemiology, *in vivo*, and *in vitro* categories are 1015, 2540, and 605, respectively. The sex of the study subject was not mentioned in 40.6% of the total number of examined entries (4160), whereas 51.6%, 28.1%, and 74.4% of the total number of entries for the epidemiology, *in vivo*, and *in vitro* categories, respectively, corresponded to NM studies.

Discussion

Animal studies provide strong evidence of disease without human epidemiological studies if the mechanism of action is relevant. Therefore sex-biased animal studies in toxicological database might lead to severe consequences, as many

Table 4. Systemic Reviews of Toxicity Data of Eight Chemicals Using Information Provided in the Three Databases

	Category	*Epidemiology*	In vivo	In vitro	*Total*
HSDB	M	54 (19.8)	78 (17.2)	3 (10.3)	135 (17.9)
	F	26 (9.5)	70 (15.5)	1 (3.4)	97 (12.8)
	MF	31 (11.4)	70 (15.5)	1 (3.4)	102 (13.5)
	NM	162 (59.3)	235 (51.9)	24 (82.8)	421 (55.8)
	Total	273	453	29	755
IRIS	M	37 (17.3)	53 (22.8)	12 (12.2)	102 (18.8)
	F	41 (19.2)	40 (17.2)	4 (4.1)	85 (15.6)
	MF	28 (31.1)	57 (24.6)	4 (4.1)	89 (16.4)
	NM	108 (50.5)	82 (35.3)	78 (79.6)	268 (49.3)
	Total	214	232	98	544
ECHA	M	78 (14.8)	512 (27.6)	54 (11.3)	644 (22.5)
	F	54 (10.2)	720 (38.8)	73 (15.3)	847 (29.6)
	MF	142 (26.9)	227 (12.2)	3 (0.6)	372 (13.0)
	NM	254 (48.1)	396 (21.3)	348 (72.8)	998 (34.9)
	Total	528	1855	478	2861
Total	M	169 (16.7)	643 (25.3)	69 (11.4)	881 (21.2)
	F	121 (11.9)	830 (32.7)	78 (12.9)	1029 (24.7)
	MF	201 (19.8)	354 (13.9)	8 (1.3)	563 (13.5)
	NM	524 (51.6)	713 (28.1)	450 (74.4)	1687 (40.6)
	Total	1015	2540	605	4160

Values are total entries of data. Values in parenthesis are percentage of each entry data.

regulatory decisions to limit or ban a chemical's use are based on animal data. Previous studies that have provided insufficient sex description of cells used in biological studies[10] reported that more than 15%, 90%, and 80% of human, mouse, and rat cell lines were sold without sex identification. Therefore, it was natural to expect that the majority (84%) of the *in vitro* data belong to NM studies. It is interesting to note that even for epidemiology data, the databases do not mention the sex of the subject.

Our study has significant limitations that are important to keep in mind. This is not an exhaustive or comprehensive review and includes primarily chemicals and data found in major toxicological database. We have summarized the database on the eight selected chemicals to reflect the current state of sex and gender consideration. The data does not address the route, timing, duration, or amount of exposure required to result in a particular condition. Some chemicals may only be toxic if inhaled, whereas others need to be ingested to be toxic. Some toxicity result from only high-dose exposures, whereas low-level exposures may be less important. Moreover, variations in the susceptibility to toxic effects, depending on the timing and duration of exposure, are not addressed.

Conclusions

In our study, the sex of the study subject was not mentioned at all in 40.6% of total studies, and only 13.5% of all studies involved both MF. To accurately evaluate the hazardous effect of chemicals, toxicity tests should be designed and conducted for both sexes, and the corresponding endpoints should cover gender concerns. Toxicity data from major toxicological databases are often considered by regulatory decision makers as important reference values for the development of regional/national chemicals guidelines or standards pertaining to human health and environmental protection. Sex- and gender-biased toxicological data might thus result in severe consequences on public health. Therefore, databases listing toxicity data as part of the open source literature should select information from MF toxicity studies.

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Author Disclosure Statement

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Supplementary Material

Supplementary Table S1
Supplementary Table S2

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