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Special article

Prioritization of NTP reproductive toxicants for field studies

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Abstract

Population studies that evaluate human reproductive impairment are time consuming, expensive, logistically difficult, and with limited resources must be prioritized to effectively prevent the adverse health effects in humans. Interactions among health scientists, unions, and industry can serve to identify populations exposed to potential hazards and develop strategies to evaluate and apply appropriate controls. This report describes a systematic method for prioritizing chemicals that may need human reproductive health field studies. Rodent reproductive toxicants identified from the National Toxicology Program (NTP) Reproductive Assessment by Continuous Breeding (RACB) protocol were prioritized on the basis of potency of toxic effect and population at risk. This model for prioritization links NTP findings with data from the National Occupational Exposure Survey (NOES) and the Hazardous Substance Data Base (HSDB) or the High Production Volume Chemical Database (HPVC) to prioritize chemicals for their potential impact on worker populations. The chemicals with the highest priority for field study were: dibutyl phthalate, boric acid, tricresyl phosphate, and *N*,*N*-dimethylformamide. © 2000 Elsevier Science Inc. All rights reserved.

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1. Introduction

Selecting chemicals for human reproductive studies generally stems from an informal network that depends on the generation of ideas from individual researchers, specific requests for assistance from workers [Health Hazard Evaluations (HHE)] [1], or from concern of potential toxicity. Often reproductive effects are studied as add-ons to studies where the population has been assembled for purposes other than for evaluation of adverse reproductive outcomes. Reproductive effect studies are expensive and logistically difficult that significantly impacts on the limited resources allocated to evaluate the enormous number of chemicals used in commerce. Although existing methods and approaches are appropriate and should continue, this report proposes an objective and systematic means to identify the most toxic compounds and highest exposed populations.

A prime focus of laboratory scientists is on the methods and techniques of their discipline that *may* serve, in a broader sense, to identify the effects of chemicals on reproduction. Often chemicals that have interesting mechanisms of action or exposure conditions generate human field studies that *may* also detect reproductive effects. This well serves the continued development of basic science, however, it does not efficiently drive applied science toward the most important issues that provide for public health. Publicly funded research programs are now being pressed to demonstrate both quality and quantity of their program effectiveness (Government Performance Review Act, GPRA). This underscores the need to provide an improved means to prioritize agents for human reproductive toxicity studies. The advances in scientific techniques (toxicology, andrology, gynecology, endocrinology, and epidemiology)

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should be matched by advances in setting priorities for studies to reduce the impact of reproductive toxicants.

Numerous reports have presented sound approaches to identify chemicals of concern, access data, develop criteria, quantitatively or qualitatively rank chemicals, and list prioritized chemical toxicants [2,3]. These reports are often established for the purpose of prioritizing chemicals for risk assessment. Some reports present and discuss criteria for setting research priorities in reproductive studies [4–6]. One report presents a screening method for identifying potential human reproductive toxicants using the NIOSH Registry of Toxic Effects of Chemical Substances and then develops an 8 h exposure level guideline [7]. Another is California's Proposition 65 (the Safe Drinking Water and Toxic Enforcement Act of 1986) that has required the development and publication of a list of prioritized reproductive toxicants for health communications [8]. The authors of Proposition 65 acknowledged an important limitation, i.e. that they were uncertain if many of their candidate chemicals are reproductive toxicants as most of them have not been evaluated in animal or human studies. Most reports attempt to provide an overall priority ranking for all possible chemicals.

One important source of potential human reproductive toxicants stems from toxicity studies conducted by the NTP. The NTP was created by an act of Congress to test chemicals that are nominated for toxicity studies in animal models. For reproductive toxicity, the RACB protocol has been shown to be an efficient and effective test of reproductive function and is the elected approach for chemicals requiring more detailed study beyond the general acute, subchronic, and chronic protocols [9]. The RACB protocol is designed to collect data on fertility in two generations, as well as data on various endpoints (reproductive and nonreproductive) before and at necropsy. Completed NTP/RACB studies on 90 chemicals have identified 43 chemicals that are reproductive toxicants in animals [10]. Of these reproductive toxicants, only a few have been evaluated in human populations.

The purpose of this report is to present ideas from a tripartite effort to establish a referenceable, prioritized listing of experimentally tested reproductive toxicants that may justify human field studies. Input stems from toxicology, epidemiology, and industrial hygiene, as represented by selected coauthors from government, industry, and labor. The authors have focused on establishing a prioritizing process for ranking reproductive toxicants that have a potential for impacting human reproductive health.

2. Methods

A consensus workshop was convened to review and reach agreement on a prioritization process for toxicants that have been evaluated by NTP. Priority ranking was based on assessment of the best currently available information and its relevance to application in human field studies. Chemicals that produce reproductive effects in animal studies at relatively low dose levels and that have large potentially exposed populations were judged to have the highest priority. Prioritization methods that apply purely objective algorithms or subjective expert panels were rejected. Additionally, it was decided not to use a final priority number/score because of concern for the precision, depth, and current quality of the databases. The general process to prioritize NTP/RACB toxicants agreed to by the attendees is as follows:

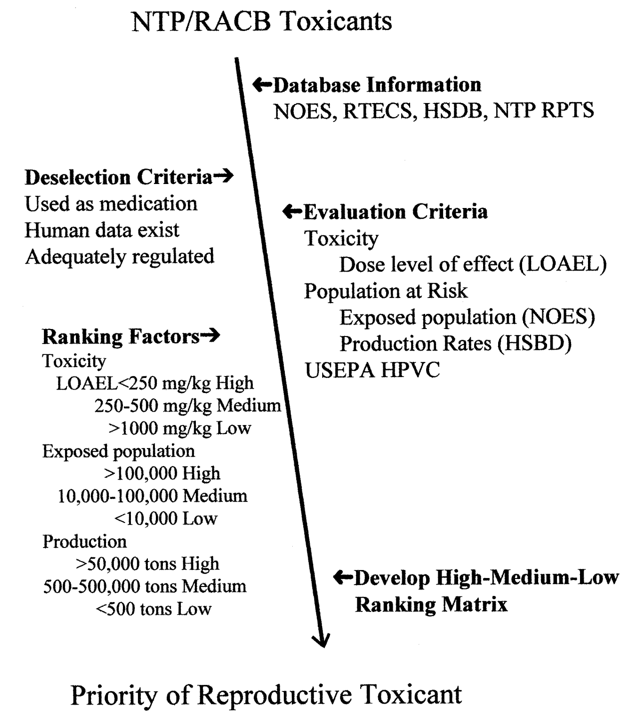

Fig. 1. Flowchart detailing the approach: identifying toxicants, exclusions, evaluation criteria, and ranking factors.

1. Use the NTP/RACB toxicants ($n = 43$) for prioritization.
2. Exclude some chemicals using a "Deselection Criteria"
3. Rank each chemical (high, medium, low) for the toxicity (high toxicity for the lowest LOAEL, low toxicity for the highest LOAEL).
4. Rank each chemical on the basis of estimated population potentially exposed.
5. Combine estimates of toxicity and population exposed to identify priority for field study.

The toxicity rankings were obtained from the lowest observed adverse effect level (LOAEL) that produced the identified reproductive endpoints in the NTP studies [10]; production data from the HSDB [12] or the High Production Volume Database (EPA); the Permissible Exposure Levels [13] from the Federal Register. Fig. 1 is a flowchart detailing the approach (identifying toxicants, exclusions, evalua-

Table 1
Sources of information

Types of information	Sources	Advantages/limitations
Animal toxicity	NTP, RACB reports	Well designed & Reviewed/LOAEL based partly on study design
Exposed worker population	NIOSH, NOES (Males, Females)	Broad coverage/not quantitative, dated
Production/use	NLM, HSDB USEPA, HPVC	Comprehensive/Secondary references
Standards/PELs	DOL, OSHA	Legal Regulation/Generally not based on reproduction

tion criteria, and ranking factors). Table 1 presents sources of information used for prioritization.

The estimates of exposed populations was obtained from the National Occupational Exposure Survey of 1983 [11]. This survey was conducted between 1980 through 1983 and derived from 4490 businesses in 98 locations. The resulting database was representative of all nonagricultural, nonmining, and nongovernmental businesses covered by the Occupational Safety and Health Act. The survey collected only observational data on potential direct workplace exposure. The major limitation includes a lack of quantitative exposure data, and the survey's progressing age.

The 43 toxicants selected for prioritization are presented in Table 2. This table presents: uses, production rates, populations potentially exposed (HSDB), lowest doses that produce adverse reproductive/developmental effects (NTP/RACB LOAEL), and the existence of exposure limits (PEL).

The NTP/RACB list contains some chemicals that have required very high levels of exposure (>2000 mg/kg/day) to produce effects. Assuming equal sensitivity across species, effects that require such high levels of exposure are unlikely to present problems in human populations. Therefore, we excluded these chemicals as well as others according to the following deselection criteria:

1. Exclude if LOAEL in NTP/RACB study is above 2000 mg/kg/day.
2. Exclude if chemical is a medication or component of a food product.
3. Exclude if chemical is one that has already been adequately studied in humans for reproductive effects.

The excluded chemicals that had LOAEL's above 2000 mg/kg/day were: diethylene glycol, 2-hydroxy-4-methoxybenzophenone, di-n-propylphthalate. The excluded drug or foodstuffs include: caffeine, carisoprodol, nitrofurantoin, nitrofurazone, phenolphthalein, propantheline bromide, theobromine, and theophylline. The chemicals deemed to have had extensive research were: 2- ethoxy-ethanol, 2-methoxyethanol, ethoxyacetic acid, ethylene glycol monoethyl ether, methoxyacetic acid, and lead acetate.

After the exclusion of certain chemicals, we reviewed, evaluated, and ranked the toxicity of the remaining 25 chemicals from the NTP/RACB summary reports [10]. The following criteria were used:

1. Assign High Priority to chemicals with LOAELs at or below 250 mg/kg/day.
2. Assign Medium Priority to chemicals with LOAELs at doses between 250 mg/kg/day and 1000 mg/kg/day.
3. Assign Low Priority to chemicals with LOAELs at or above 1000 mg/kg/day.

The lowest adverse effect level for an endpoint was taken from the three dose levels actually used in the study (LOAEL). Significance was determined based on the nature of effects including: infertility, impaired gestational outcomes, malformations and impaired sperm parameters, or estrous cycle. A review for other less significant effects such as "histopathologically detectable" changes was factored in to the ranking decision. Additionally, dose-related effects, and mode of action were considered. As the purpose of this exercise was to prioritize chemicals for future human field studies exclusively, second generation effects were not as highly ranked.

The estimate of potentially exposed workers was based on evaluation of the NOES and HSDB databases. The ranking criteria was as follows:

1. Assign high rank if estimated exposure is over 100 000 workers.
2. Assign medium rank if estimated exposure is between 10 000 and 100 000 workers.
3. Assign low rank if estimated exposure is less than 10 000 workers.
4. Use production rates if NOES data were missing or if NOES estimated less than 10 000 workers to modify categorical rank as follows:

   High Production Rate = > 500 000 tons
   Medium Production Rate = 500 to 500 000 tons
   Low Production Rate = < 500 tons

5. A few chemicals do not have exposure survey data or production data and, therefore, were ranked low. (We recognize that this does not preclude their toxicity in humans, but from a practical viewpoint it is difficult to justify a high ranking in the absence of exposure data.)

Table 2
Toxicants selected for prioritization

	Chemical (* = excluded)	CAS	Use	Production (Tons)	NOES Total	RACB LOAEL (mg/kg/d)	PEL
1	1,2,3-trichloropropane	96-18-4	paint remover	10,564	492	30	50 ppm
2	2,2 bis(BM)1,3-propanediol	3296-90-0	flame retard.	1,107	no data	274	no std
3	2-butoxyethanol	111-76-2	solvent	135,463	2,132,292	720	50 ppm
4	2-ethoxyethanol*	110-80-5	solvent	79,622	264,440	1500	200 ppm
5	2-hydroxy-4-methoxybenzophenone*	131-57-7	sunscreen prep	539	27,518	4000	no std
6	2-methoxyethanol*	109-86-4	solvent	37,203	168,185	159	25 ppm
7	4-chloronitrobenzene	100-00-5	ag. chem. prod.	1,443	2,950	125	1 mg/m3
8	Acrylamide	79-06-1	reactive monomer	39,914	10,653	3.2	0.03 mg/m3
9	bisphenol A	80-05-7	plasticizer	503,280	92,136	437	no std
10	Boric acid	10043-35-3	paper/insecticide	138,767	492,618	145	no std
11	Caffeine*	58-08-2	medication	2,008	19,939	12.5	no std
12	Carisoprodol*	78-44-4	medication	44	2,432	–	no std
13	Dibutyl phthalate	84-74-2	solvent	8,500	512,626	65	5 mg/m3
14	diethylene glycol*	111-46-6	solvent	390,625	890,123	6125	no std
15	Di-n-hexylphthalate	84-75-3	plasticizer	no data	7,149	380	no std
16	Di-n-pentylphthalate	131-18-0	plasticizer	no data	no data	760	no std
17	Di-n-propylphthalate*	131-16-8	plasticizer	446	no data	4060	no std
18	ethoxyacetic acid*	627-03-2	metab. EGEE	no data	no data	303	no std
19	Ethylene glycol monoethyl ether acetate*	111-15-9	solvent	48,678	265,098	1860	100 ppm
20	Ethylene glycol	107-21-1	antifreeze	2,615,000	1,511,020	850	50 ppm
21	Ethylene glycol monophenyl ether	122-99-6	solvent	3,403	111,039	1875	no std
22	Formamide	75-12-7	solvent	899	2,734	172	20 ppm
23	lead acetate trihydrate*	301-04-2	dying/printing	223	2,145	700	50 μg/mg
24	m/p-Cresol	1319-77-3	disinfectants	1,597	26,929	1500	5 ppm
25	methoxyacetic acid*	625-45-6	metabl. EGMEE	no data	no data	140	no std
26	Methyl salicylate*	119-36-8	solvent	40	454,800	500	no std
27	M-Nitrobenzoic acid	121-92-6	dye	680	no data	1300	no std
28	N,N-dimethylformamide	68-12-2	solvent	25,766	124,679	200	10 ppm
29	N,N-methylenebisacrylamide	110-26-9	cross linking agent	no data	66	1.6	no std
30	N-hydroxymethylacrylamide	924-42-5	sunscreen prep.	4,600	20,666	13	no std
31	Nitrofurantoin*	67-20-2	medication	no data	3,755	180	no std
32	Nitrofurazone*	59-87-0	antibacterial agent	<1	6,653	15	no std
33	Oxalic acid	144-62-7	cleaning agent	2,352	142,005	275	1 mg/m3
34	Phenolpthalein*	77-09-8	laxative	<1	75,244	1000	no std
35	p-Nitrobenzoic acid	62-23-7	dye	680	42,703	500	no std
36	Propantheline bromide*	50-34-0	medication	no data	2,157	760	no std
37	Sulfamethazine	57-68-1	antibacterial	667	17,376	1450	no std
38	Theobromine*	8002-88-0	cocoa, vasodilator	no data	no data	126	no std
39	Theophylline*	58-55-9	medication	no data	29,721	126	no std
40	Tricresyl phosphate	1330-78-5	plasticizer	830	239,510	62.5	no std
41	Triethylene Glycol Dimethyl Ether	112-49-2	N/A	no data	270	87.5	no std
42	Tris-(2-chloroethyl)phosphate	115-96-8	fire-retd. plasticizer	855	5,100	350	no std.
43	Vinylcyclohexene	100-40-3	polymer	1,443	No data	500	no std

3. Results

Table 3 presents the data used to estimate toxicity including nature of reproductive effects, doses, and rank for the toxicity evaluation. The toxicants demonstrating significant toxicity at doses less than 250 mg/kg are di-n-pentylphthalate, di-n-hexylphthalate, formamide, 1,2,3-trichloropropane, triethylene glycol dimethyl ether, *N*,*N*-methylenebisacrylamide, 4-chloronitrobenzene, acrylamide, N–hydroxymethylacrylamide, dibutyl phthalate, boric acid, tricresyl phosphate, and *N*,*N*-dimethylforamide. Of these toxicants, dibutyl phthalate, boric acid, tricresyl phosphate and *N*,*N*-dimethylformamide have both high populations potentially exposed and high toxicity.

Table 4 presents the data and rankings for the estimation of population exposed. The table lists the NOES estimate of exposed workers and the estimates of production rate. Where more current production rate data are available from USEPA High Production Volume chemical database they are listed and noted. The final categorical rank for each chemical toxicant is noted in the last column. The toxicants with an estimated exposure over 100 000 workers are 2-butoxyethanol, ethylene glycol, dibutyl phthalate, boric acid, tricresyl phosphate, oxalic acid, *N*,*N*- dimethylformamide, and ethylene glycol monophenyl ether. To combine the rankings for toxicity and population at risk, a matrix of the final categorical rankings for estimated toxicity and estimated population at risk was developed in Table 5. The four

Table 3
Estimate of toxicity

Toxicant (CAS #)	Nature of effect (male/female/dev)	Dose-NTP/RACB (LOAEL) <250 mg/kg/d—high 250–1000 mg/kg/d—medium >1000 mg/kg/d—low	Rank lo-med-hi (male-female-dev)
2-Butoxyethanol	Male—reduced testis wgt	1350 mg/kg/d	Medium
(111-76-2)	Female—		(M,F,D)
	Dev—reduced pup wgt/litter	720 mg/kg/d[a]	
Ethylene Glycol	Male—reduced sperm count; reduced testis wgt	850 mg/kg/d[a]	Medium
(107-21-1)	Female—		(M,F,D)
	Dev—reduced # live pups; & pup wgt/litter	850 mg/kg/d	
Dibutyl Phthate	Male—reduced testis wgt; accessory gland wgt, reduced sperm count	650 mg/kg/d	High
(84-74-2)	Female—		(M,F,D)
	Dev—reduced # live pups; & pup wgt/litter	65 mg/kg/d[a]	
Boric Acid	Male—reduced sperm motility	145 mg/kg/d[a]	High
(10043-35-3)	Female—reduced estrous cycle length	145 mg/kg/d	(M,F,D)
	Dev—reduced pup wgt/litter	145 mg/kg/d	
Tricresyl Phosphate	Male—reduced sperm motility, & morphology	62 mg/kg/d[a]	High
(1330-78-5)	Female—		(M,F,D)
	Dev—reduced mean # litters/pair	62 mg/kg/d	
Oxalic acid	Male—reduced sperm morphology, & prostate wgt	275 mg/kg/d[a]	Medium
(144-62-7)	Female—		(M,F,D)
	Dev—reduced # live pups/litter; & pup wgt/litter	275 mg/kg/d	
N,N-Dimethylformamide	Male—reduced testis, epididymal & prostate wgt	200 mg/kg/d[a]	High
(68-12-2)	Female—		(M,F,D)
	Dev—reduced pup wgt/litter	200 mg/kg/d	
Ethylene Glycol Monophenyl Ether	Male—reduced testis & seminal vesicle wgt	1875 mg/kg/d[a]	Low
(122-99-6)	Female—Affected sex in crossover		(M,F,D)
	Dev—reduced mean # litters; & pup wgt/litter	1875 mg/kg/d	
Bisphenol A	Male—reduced seminal vesicular & epididymal wgts	437 mg/kg/d[a]	Medium
(80-05-7)	Female—		(M,F,D)
	Dev—reduced mean # litters/pair & # of live pups	875 mg/kg/d	
p-Nitrobenzoic Acid	Male—reduced seminal vesicular & epididylmal wgts	500 mg/kg/d[a]	Medium
(62-23-7)	Female—affected sex from crossover	1100 mg/kg/d	(F,D)
	Dev—reduced pup wgt/litter	500 mg/kg/d	
M/P Cresol	Male—reduced testis & semineferous vesicular wgts	1500 mg/kg/d[a]	Low
(1319-77-3)	Female—		(M,F,D)
	Dev—reduced # live pups & pup litter wgts	2100 mg/kg/d	
N–Hydroxymethyl-acrylamide	Male—increased sem. ves. wgts & sperm motility	13 mg/kg/d[a]	High
(924-42-5)	Female—		(M,F,D)
	Dev—reduced # live pups	17 mg/kg/d	
Sulfamethazine	Male—reduced sem. ves. wgt.	1450 mg/kg/d[a]	Low
(57-68-1)	Female—		(M,F)
	Dev—reduced mean # litters/pair reduced # live pups & pup litter wgts	1450 mg/kg/d (incomplete study)	
Acrylamide	Male—reduced prostate wgt.	3.2 mg/kg/d	High
(79-06-1)	Female—		(M,D)
	Dev—reduced # live pups	7.2 mg/kg/d	
Di-N-Hexylphthalate	Male—reduced testis & accessory gland wgts & sperm counts and motility	1670 mg/kg/d	High[b]
(84-75-3)	Female—		(M,F,D)
	Dev—reduced mean # litters/pair, & # live pups & pup litter wgts & increased # days to litter	380 mg/kg/d[a] (PUSH to HI)	
Tris (2-Chloroethyl) Phosphate	Male—reduced testis wgt & sperm count, motility, morphology	700 mg/kg/d	Medium
(115-96-8)	Female—		(M,F,D)
	Dev—reduced # live pups & litters/pair	350 mg/kg/d[a]	
4-Chloronitrobenzene	Male—reduced sem. ves. wgt	250 mg/kg/d	High
(100-40-3)	Female—increased estrous length	250 mg/kg/d	(M,F,D)
	Dev—reduced pup litter wgt	125 mg/kg/d[a]	
Formamide	Male—reduced sem. ves. wgt	172 mg/kg/d[a]	High
(75-12-7)	Female—increased estrous cycle length	218 mg/kg/d	(M,F,D)
	Dev—reduced # live pups & reduced mean # litters/pair	218 mg/kg/d	

(continued on next page)

Table 3 *(continued)*

Toxicant (CAS #)	Nature of effect (male/female/dev)	Dose-NTP/RACB (LOAEL) <250 mg/kg/d—high 250–1000 mg/kg/d—medium >1000 mg/kg/d—low	Rank lo-med-hi (male-female-dev)
1,2,3 Trichloropropane (96-18-4)	Male—reduced sperm count	120 mg/kg/d	High (M,F,D)
	Female—increased estrous cycle length	30 mg/kg/d[a]	
	Dev—reduced mean litters/pair, & # live pups, & days to litter	120 mg/kg/d	
Triethylene glycol dimethyl ether (112-49-2)	Male—		High (F,D)
	Female—affected sex in crossover	87.5 mg/kg/d	
	Dev—reduced pup wgt/litter, & days to litter	87.5 mg/kg/d	
N,N-Methylenebisacrylamide (110-26-9)	Male—reduced sperm motility & reduced testis wgt	1.6 mg/kg/d[a]	High (M,F,D)
	Female—		
	Dev—dominant-lethal-males/females & # live pups reduced pup wgt/litter	4.7 mg/kg/d	
M-Nitrobenzoic acid (121-92-6)	Male—		Low (M,F,D)
	Female—affected sex in crossover	1300 mg/kg/d[a]	
	Dev—reduced # live pups/litter, & pup wgt/litter	1300 mg/kg/d	
Di-N-Pentylphthalate (131-18-8)	Male—reduced testis, epidid., & prostage wgt, reduced sperm count	4800 mg/kg/d	High[b] (M,F,D)
	Female—		
	Dev—reduced # litters/pair, & # live pups/pair, increased days to litter	760 mg/kg/d[a] (“other Info” > Push to High)	
2,2,Bis(BM) 1,3-propanediol (3296-90-0)	Male—		Medium (M,F,D)
	Female—affected sex in crossover	274 mg/kg/d[a]	
	Dev—reduced pup wgt/litter	274 mg/kg/d	
Vinylcyclohexene (100-40-3)	Male—		Medium (M,F,D)
	Female—induced oocyte death	500 mg/kg/d[a]	
	Dev—reduced pup wgt./litter		

[a] LOAEL, lowest observed adverse effect level.
[b] Additional data push to high.

chemicals with the highest priority for field study are: dibutyl phthalate, boric acid, tricresyl phosphate, and *N*,*N*-dimethylformamide.

4. Discussion

The priorities established in this report were derived from a process based on two primary criteria: the estimated toxicity and estimated population size at risk. Specifically, this process links National Toxicology Program study findings with data from the NOES (NIOSH) and HSDB (NLM) or HPVC (USEPA) to select candidates with a high potential toxicity and a high probability of worker exposure. The application is directed at field studies to evaluate the possible impact of their identified toxicity on human populations. The resources of the National Toxicology Program to identify chemical toxicants can serve as a guide for human health evaluation, if a more concrete linkage is established to initiate studies that have impact on human populations. This effort to prioritize reproductive toxicants is proposed to provide a systematic basis for selection of those chemical exposures most likely to impair reproductive health.

The design of a priority system must consider, at a minimum, the type and quality of informational resources available, how the information can be used for the purposes identified, and the methods used to process the information. At some point acceptance of the available data must be made even though it may be imperfect. The ideal process yields an objective, integrative, ranking that is clear, referenceable, and defensible. It should reflect the input of knowledgeable health scientists such that others will want to use the outcome. The system should also demonstrate awareness of informational gaps and make recommendations to enhance the future objectives of the system. It is hoped that this report will serve to guide field study research to chemical agents that have a high probability of causing reproductive impairment.

The first limitation in any priority system is the initial selection of candidate agents. Other groups have developed their lists from the universe of chemicals that may be required if their purposes include broad applications (environmental, marine, wildlife, etc.). Such broad applications require the inclusion of many chemicals regardless of whether they have been demonstrated to be a significant known toxicant relevant for prioritization. The NTP/RACB list reflects reproductive toxicants that have surfaced as chemicals proven to be harmful to reproduction in animals.

Our review of the data sources for these criteria presented some concerns that motivated the authors to soften the strict objective application of a mathematical algorithm. It was felt that some judgment was needed for the applica-

Table 4
Estimate of population exposed

Toxicant (CAS #)	NOES >100,000 Worker (high) >10,000 Workers (medium) <10,000 Workers (low)	Production >500,000 Tons (high) 500–500,000 (medium) <500 Tons (low)	Rank
2-Butoxyethanol (111-76-2)	2,132,000	135,463	High
Ethylene glycol (107-21-1)	1,511,000	2,615,000	High
Dibutyl Phthate (84-74-2)	512,000	8,500	High
Boric Acid (10043-35-3)	489,700	138,767	High
Tricresyl Phosphate (1330-78-5)	239,500	830–1,115[a]	High
Oxalic acid (144-62-7)	142,000	2,352–3,944[a]	High
N,N-dimethylformamide (68-12-2)	125,000	25,766–51,833[a]	High
Ethylene Glycol Monophenyl Ether (122-99-6)	111,000	3,403–4,809[a]	High
Bisphenol A (80-05-7)	92,000	503,280–716,593[a]	High
p-Nitrobenzoic Acid (62-23-7)	42,700	680	Medium
M/P Cresol (1319-77-3)	M-Cresol = 5,600 P-Cresol = 21,300	M-Cresol = 1,500 P-Cresol = No Data	Medium
N-Hydroxymethylacrylamide (924-42-5)	20,700	4600	Medium
Sulfamethazine (57-68-1)	17,400	667	Medium
Acrylamide (79-06-1)	10,600	39,914–55,973[a]	Medium
Di-n-hexylphthalate (84-75-3)	7,100	No Data	Low
Tris(2-Chloroethyl) Phosphate (115-96-8)	5,100	855–1,304[a]	Low
4-Chloronitrobenzene (100-40-3)	2,950	1,443–2,619[a]	Medium[b]
Formamide (75-12-7)	2,700	899–1,304 (USEPA HPVC)	Low
1,2,3 Trichloropropane (96-18-4)	490	10,564–15,417 (USEPA HPVC)	Low
Triethylene glycol dimethyl ether (112-49-2)	270	No Data	Low
N,N-methylenebisacrylamide (110-26-9)	66	No Data	Low
m-Nitrobenzoic acid (121-92-6)	4300	680	Low
Di-n-pentylphthalate (131-18-8)	No Data	No Data	Low[c]
2,2,bis(BM) 1,3-propanediol (3296-90-0)	No Data	1,107–2,473[a]	Medium
Vinylcyclohexene (100-40-3)	No Data	1,443–2,619[a]	Low[c]

[a] EPA HPVC U.S. Environmental Protection Agency High Production Volume Chemical database http://wwwepa.gov/opptintr/chemtest/hazchem.htm).
[b] adjusted based on production rate.
[c] Low rank baesd on lack of NOES data.

tion of NOES and NTP/RACB data. As previously discussed, the NOES is dated and may not offer the precision desirable to determine the current population at risk. However, NIOSH has found that for high production volume chemicals that have continued in use, the data in the Chemical Marketing Report (e.g. borates, chemical profile, September 1, 1997 [14]) and the Chemical and Economics Handbook [15] suggest that the uses remain substantially

Table 5
Priority matrix

Categorical ranking	Estimated population at risk		
	Low	Medium	High
Estimated Toxicity			
Low	M-Nitrobenzoic acid	Sulfamethazine, M/P cresol	Ethylene glycol monophenyl ether
Medium	Tris(2-chloroethyl)phosphate Vinylcyclohexene	P-Nitrobenzoic acid, 2,2,bis(BM) 1,3-propanediol	2-Butoxyethanol Oxalic acid Bisphenol A Ethylene glycol
High	Di-n-Pentylphthalate Di-n-Hexylphthalate, Formamide 1,2,3-Trichloropropane Triethylene glycol dimethyl ether N,N-Methylenebis acrylamide	Acrylamide, N-Hydroxymethylacrylamide 4-Chloronitrobenzene	Dibutyl phthalate Boric acid Tricresyl phosphate N,N-Dimethylformamide

the same, indicating that the potential exposure estimates still have validity for the comparative approach we have used. Certainly the exposure data will be incorrect for chemicals used in new processes. This is the most significant limitation in our effort to prioritize the chemicals. An additional complexity stems from exposures where the chemical in question is a component of the overall exposure to a complex mixture. The NTP and NIOSH have recognized this and have established an interagency effort to enhance exposure assessments including an updating of the NOES database [16]. Recognizing these limitations, we added production rate data from HSDB to enhance or strengthen this ranking criteria. Production rates however, do not identify whether potential exposures arise from open or closed systems, or add to quantitative environmental levels. Although potential worker exposures do not necessarily track production volumes, the volume is a useful surrogate for new chemicals or new uses of chemicals.

The summarized NTP/RACB findings [10] present doses selected during the design phase of the study and their associated effects do not necessarily present the true dose-response relationships. So, here too, we applied expert judgment in the final rankings. Our evaluation of “significant effects” was based on the nature of effects as noted in the report summary tables. Frank effects such as malformations and infertility were considered more important than only histologic detectable changes. Additionally, dose related effects and mode of action were considered important. Ultimately, we used Low-Medium-High categories to group the toxicants rather than attempting to reduce the priority to a numerical score. It did not seem convincing during the consensus workshop that we had the precision to distinguish between close numerical scores. Although each of these information sources have limitations (Table 2), they currently provide the best available information.

The only other prioritized list of potential reproductive toxicants was developed by the State of California [7]. Candidate reproductive and developmental toxicants were prioritized by the California Department of Health Services in response to their Proposition 65 (The Safe Water and Toxic Enforcement Act of 1986). A scientific advisory panel identified 164 candidate chemicals from the published literature, by agencies, by experts, and the Modified Hazardous Air Pollutant Prioritization System (obtained for the Registry of Toxic Effects of Chemical Substances [15]). Based on an evaluation by their expert panel considering the potential for exposure and perceived hazard, 42 chemicals were selected for final prioritization. Thirteen members of the expert panel then scored each of the chemicals. The top five chemicals were arsenic, cadmium, formaldehyde, vinyl chloride, and aldrin. Three of their prioritized chemicals are also listed in our prioritization (acrylamide, boric acid, and formamide). Interestingly, they excluded phthalates from their list because they represented a group of chemicals rather than a discrete chemical. In addition, they pointed out that prioritization processes will be biased for chemicals that have exposure data and they recommended that future prioritizations should consider using data bases such as the National Occupational Exposure Survey. Because on the infusion of new information on chemicals that affect reproduction, they recommended that priority lists need updating at regular intervals. To date, they have not published an updated priority list.

OSHA permissible exposure limits exist for only 14 of the 43 prioritized reproductive toxicants listed in Table 1 and none of them used reproductive hazards as a basis for the PEL. The four highest ranked chemicals on the basis of toxicity and potentially exposed worker populations are dibutyl phthalate, boric acid, tricresyl phosphate, and *N*,*N*-dimethyl formamide. Dibutyl phthalate and *N*,*N*-dimethyl formamide have OSHA permissible exposure limits, the other two do not. Although NIOSH has conducted a few health hazard evaluations on these substances, none of these evaluations has included health based laboratory assessments for reproductive effects. A review of the published literature indicates that these potential toxicants have not been adequately evaluated for reproductive effects in exposed workers.

A credible mechanism for linking hazard identification stemming from animal toxicology studies with priorities for human field studies needs to be developed and a viable, dynamic system for communication and interaction among health scientists, labor, and industry needs to be established. Partnering from both industry and unions experts should initiate predecisional involvement and cooperation to assess the possible impact of reproductive toxicants on exposed populations. Institutions providing research funding grants should use this prioritized information to request relevant proposals for the conduct and evaluation of human field studies. Joint efforts would yield updated, published lists prioritizing animal reproductive toxicants that, in turn, would serve as a guide to the identification of worker populations exposed to these potential hazards and priorities for evaluation, control, and prevention of adverse reproductive effects.

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