Environmental Factors in Breast Cancer

Supplement to ***Cancer***

Chemicals Causing Mammary Gland Tumors in Animals Signal New Directions for Epidemiology, Chemicals Testing, and Risk Assessment for Breast Cancer Prevention

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Identifying chemical carcinogens in animal studies is currently the primary means of anticipating cancer effects in humans. Animal studies to evaluate potential chemical carcinogenicity are particularly important for breast cancer because environmental and occupational epidemiologic research is sparse. Chemicals that increased mammary gland tumors in animal studies were compiled from the International Agency for Research on Cancer (IARC), the U.S. National Toxicology Program (NTP), and other sources. Summary assessments of the carcinogenic potential for each chemical and potentially exposed populations were also compiled. In all, 216 chemicals were identified that have been associated with increases in mammary gland tumors in at least 1 study. These include industrial chemicals, chlorinated solvents, products of combustion, pesticides, dyes, radiation, drinking water disinfection byproducts, pharmaceuticals and hormones, natural products, and research chemicals. Twenty-nine are produced in the U.S. at >1 million pounds/year; 35 are air pollutants, 25 have involved occupational exposures to >5000 women, and 73 have been present in consumer products or as contaminants of food. Thus, exposure is widespread. Nearly all of the chemicals were mutagenic and most caused tumors in multiple organs and species; these characteristics are generally believed to indicate likely carcinogenicity in humans. To our knowledge, this is the most comprehensive list developed of animal mammary gland carcinogens and, along with associated data, is publicly available at URL: www.silentspring.org/sciencereview and at URL: www.komen.org/environment. Valuable information from cancer bioassays is not well utilized in risk assessment and regulatory processes, suggesting a need to strengthen chemicals testing and risk assessment as tools for breast cancer prevention. ***Cancer*** **2007;109(12 Suppl):2635–66.** © *2007 American Cancer Society.*

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GOALS

Breast cancer is the most common invasive malignancy among women in the U.S. and the leading cause of death in women from their late 30s to their early 50s.[1] Identifying breast carcinogens could lead to risk reduction. Human carcinogens have largely been identified in occupational studies, which provide little information concerning women's cancers because most of the studied popula-

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tions have been male. Experimental studies in animals offer an alternative means for identifying potential carcinogens. Despite unresolved questions regarding their human relevance, animal studies are a key source of information, given that epidemiologic studies require a large number of women, a long duration, high costs, and substantial—often unattainable—exposure information.

More than 80,000 chemicals are registered by the U.S. Environmental Protection Agency (U.S. EPA) as being in commerce in the U.S., and of these, a small fraction have been tested in animals to evaluate carcinogenic potential.[2,3] To deepen our understanding of what these animal studies can tell us regarding environmental pollutants that may cause breast cancer, we compiled a list of chemicals that increased mammary gland tumors in test species. We collected data regarding mutagenicity, opportunities for exposure, and other characteristics of chemical use, source, and regulation. In addition, for a subset of chemicals we reviewed experimental details and study interpretation to identify opportunities to improve testing and data utilization. Although chemicals on this list vary in the strength of evidence that they cause mammary gland tumors, this list builds on previous work by others[2,4,5] and provides a new tool for prioritizing further research and policy in support of breast cancer prevention.

We had 2 primary goals. The first was to lay the groundwork for new epidemiologic studies of breast cancer. We hope to suggest new hypotheses, focus human research on chemicals with stronger animal evidence and more widespread exposures, stimulate improved exposure measurement, and identify highly exposed populations for study. We also hope to encourage cross-disciplinary collaborations by making toxicology data that are relevant to breast cancer etiology available to epidemiologists and physicians. Better integration of these disciplines will lead to stronger study designs, for example, by reducing the common occurrence of occupational cohorts that include women but fail to report data for breast cancer even though they are studying exposures to chemicals that cause mammary gland tumors.[6–9]

Second, we seek to strengthen the practice of toxicology, including animal testing and risk assessment, as a tool for breast cancer prevention. Focusing on the mammary tumor endpoint may identify ways to strengthen chemical screening and testing, and improve interpretation of data from these tests in order to maximize the relevance to human breast cancer. In addition, information on chemical mammary gland carcinogens is valuable for regulators to consider in limiting human exposure and for manufacturers to evaluate as a basis for reformulating products or re-engineering processes to avoid these chemicals.

Because of the cross-disciplinary nature of this article, we have included an introductory review of issues related to the relevance of the animal bioassays to human exposure scenarios, including extrapolation from high doses in animal studies to the lower doses expected in humans. Our review of these topics is brief, but readers can turn to referenced documents for more detailed discussion.

STRENGTHS AND LIMITATIONS OF ANIMAL MODELS TO PREDICT HUMAN CANCER RISKS

Animal models of chemically induced cancer are the primary means of understanding and anticipating effects of chemicals in humans. For therapeutic agents, animal studies guide development before human clinical trials. For commercial chemicals and pollutants, particularly when human data are not available, they guide prevention strategies to reduce environmentally associated cancers by reducing exposures.[10,11]

A typical bioassay conducted by the U.S. National Toxicology Program (NTP) doses male and female mice and rats for 2 years and then counts tumors in all organs. Usually there are controls and 3 dose groups with 50 animals per group. To detect increased tumors in these small groups of animals, dose levels are necessarily higher than would be expected in human exposure scenarios. The bioassay is designed to identify genotoxic carcinogens, although some chemicals induce positive responses in this test through nongenotoxic mechanisms; it is unlikely to identify many nongenotoxic carcinogens that act as promotors, or by altering tissue structure during development,[12] or by transgenerational epigenetic phenomena.[13] This NTP bioassay is currently considered the best way to identify potential human carcinogens, but it is an expensive screening tool at over $2 million per test chemical.

Use of animal studies to identify human carcinogens is supported by observations regarding the overall concordance of human studies with animal tests. All known human carcinogens that have been tested in animals are also carcinogenic in animal models and have at least 1 common organ site in both humans and the animal model.[14–16] Historically, approximately one-third of known human carcinogens were shown to be carcinogenic in animals before being confirmed as carcinogens in epidemiologic studies.[16,17] Based on these and other findings, the International Agency for Research on Chemicals (IARC) has concluded that "it is biologically plausible that

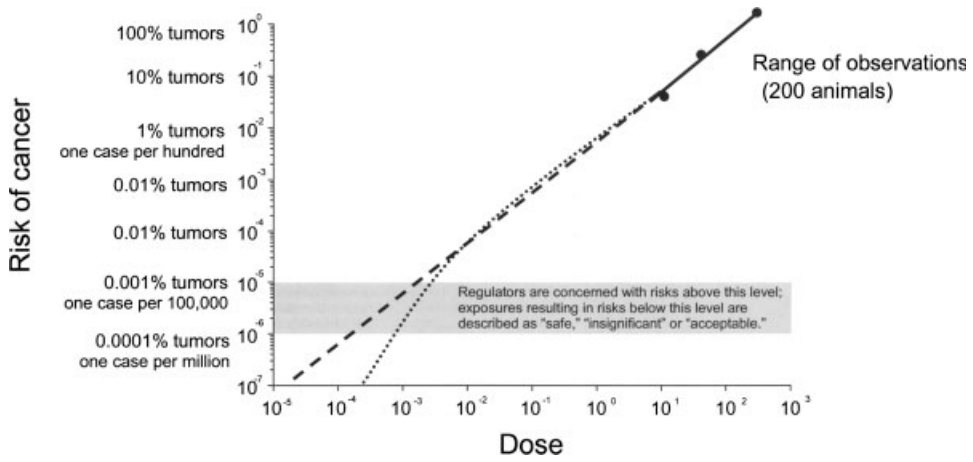

FIGURE 1. High-dose to low-dose extrapolation. This figure illustrates the gap between the risk, or frequency, of tumors observed in animal cancer assays (5–100%) and the risk range that is typically of interest in environmental regulation (1 extra case per 100,000 or million persons exposed). The 2 dashed/dotted lines extending from the observed data to the low-risk/low-dose corner of the graph are examples of different extrapolations that can be made depending on assumptions regarding relevant mechanisms of action for the chemical. The choice of extrapolation affects the dose associated with target cancer risks of 1 per million. The shaded area identifies the range of risks that are typically treated as de minimus—risks above which regulation is considered to reduce exposure and below which exposure is described as 'safe' or posing 'insignificant' risk.

agents for which there is sufficient evidence of carcinogenicity in experimental animals also present a carcinogenic hazard to humans . . ." and "in the absence of additional scientific information, these agents are considered to pose a carcinogenic hazard to humans."[17] However, it cannot be assumed that just because most human carcinogens are also rodent carcinogens the converse is true,[18,19] so the strength of evidence from animal studies is interpreted as an indication of the likelihood that the chemical will be a human carcinogen.

Narrower inferences—that a chemical is not just carcinogenic, but carcinogenic in a specific target organ—are more tentative because target organs for carcinogens are not necessarily the same across species. Thus, whereas it is likely that chemicals that cause mammary tumors in rats will also cause tumors in some organ in mice and humans, the mammary gland will not necessarily be the target in all species.[18,20] Agents that cause tumors in rodents in any hormonally responsive tissue might be considered potentially relevant to human breast cancer[11]; however, for this first project to identify potential human breast carcinogens we began by identifying only animal mammary gland carcinogens. Characterizing the relevance of various rodent models specifically to human breast cancer is still an area of active research.[21]

Inference from experimental to human dose scenarios is another area of uncertainty. The observed relation between dose and frequency of tumors in animal studies is used to estimate exposure levels that would be associated with much lower tumor frequency in humans. Figure 1 illustrates that this practice typically requires extrapolating from doses causing tumors in 5% to 100% of animals down to doses expected to cause tumors in 0.001% to 0.0001%. These low tumor frequencies correspond to risks that are typically of concern for human chemical exposures (ie, an estimated risk that 1 person in 100,000 or 1,000,000 exposed for a lifetime would develop cancer from the exposure). This high-to-low-dose extrapolation is necessary in animal toxicology studies because millions of animals would otherwise be required in an experiment designed to show statistically significant increased tumors in the range of 0.001% to 0.0001%. Although this level of individual risk may appear to be small, it can be significant at the population level. For example, if there is a small cancer risk associated with a flame retardant in children's pajamas, and millions of children are wearing these pajamas, this exposure may result in a socially unacceptable number of new cancers.

The assumption of linearity in high-to-low-dose extrapolation in animal bioassays is derived from biologically based models of cancer risk associated with radiation and other genotoxic agents. This model rests on the well-supported theory that for mutagens there is some risk of causing a mutation at any dose, no matter how low, and that the risk of mutation, and subsequently cancer, is linearly related to the dose.[22] At the same time, it is important to acknowledge that there are substantial uncertainties in extrapolating orders of magnitude below the observable data, espe-

cially because mechanisms of action, and associated dose-response relations, can change across the dose range.[23]

The considerable debate on the relevance of high-dose tests in animals for evaluating carcinogenic risks in humans revolves around 2 major issues. First, for some chemicals tumors in the high-dose tests may be secondary to toxicity that is caused at high doses, so tumor formation would not be expected at low doses (for example, because tissue damage or saturation of detoxification enzymes occurs at higher doses but not lower doses, and the chemical is not mutagenic or is a weak mutagen).[23] Following this line of reasoning, there may be no cancer risk from exposure below threshold levels that cause observed toxicity in animals. For example, the U.S. EPA recently revised its risk assessment for the disinfection byproduct chloroform in drinking water based on the view that there is a threshold dose below which there is no cancer risk.[24] Figure 1 shows how high-to-low-dose extrapolation might look for linear (dashed) or threshold (dotted) dose-response assumptions. Exposure limits based on linear extrapolation are generally much lower (stricter) than those based on assumption of a threshold.

The second issue is that some chemicals appear to cause cancer in animals by a mechanism that is not shared by humans, so the chemical would not be expected to be carcinogenic in humans.[25,26] For example, some chemicals appear to cause tumors in the male mouse kidney only, by a mechanism that appears not to be relevant to humans[27] (although some disagree with this conclusion).[28]

In both these cases—in which the carcinogenicity is believed to be secondary to toxicity or the carcinogenic effect is considered not relevant to humans—the revised exposure guideline is based on the threshold for toxicity,[25] a more permissive standard than a carcinogenicity standard based on linear extrapolation to low effect levels. Disproportionate financial resources have been dedicated to supporting arguments that the carcinogenicity in animal studies is due to toxicity that occurs only at high doses or through biological mechanisms that are not relevant to human exposure scenarios (false-positive) with an aim to reduce regulatory constraints and increase public skepticism of the relevance of animal toxicity studies.[10,29]

Conversely, comparable resources are not extended to evaluate how chemical testing and risk assessment as currently practiced may miss critical adverse effects (false-negatives) or fail to identify needed data that are not available (omissions). For example, the cancer bioassay may lead to false-negatives because: 1) animal species/strains that are used do not reflect the range of human sensitivity; 2) tests typically do not include younger (developing) animals, which are uniquely sensitive; 3) the study duration is too short to identify tumors with longer latency; or 4) studies do not identify effects of chemical interactions because they test 1 chemical at a time.[5,12,25,30] In addition, omissions arise because the cancer bioassay is resource-intensive, so most chemicals, including most chemicals in common use, have not been evaluated to determine if they are carcinogens,[2,3] and risk assessments only consider chemicals for which a cancer potency estimate has been derived, but these estimates are available for just a small fraction of chemicals shown to be carcinogenic in animal studies.

Because the testing required to rule out false-negative results is essentially infinite, ultimately chemicals policy involves choosing to either 1) accept the possible (and uncertain) health risks by allowing exposure or 2) reject the possible health risks by preventing the exposure. The decision to reduce uncertainty by collecting additional information is always accompanied by a decision to accept or reject the potential risk, at least while new information is being collected. In current regulatory decision-making, little effort is made to characterize uncertainty associated with omissions and false-negative results or to be explicit regarding how much uncertainty about potential health risks is acceptable for a given chemical use or exposure.

MATERIALS AND METHODS

To make information regarding chemical mammary gland carcinogens readily accessible, we developed a database of exposure and carcinogenicity data for chemicals that showed increases in these tumors.[31] The database is freely available at URL: www.silentspring.org/sciencereview and at URL: www.komen. org/environment.

Identification of Chemicals Associated With Increased Mammary Gland Tumors

Chemicals were identified as mammary gland carcinogens because at least 1 study showing increased mammary gland tumors was reported in one of the following sources: Carcinogenic Potency Database (CPDB),[32] IARC Monographs summaries,[33] National Toxicology Program (NTP) Technical Reports,[34] NTP 11th Report on Carcinogens (11th ROC),[35] and Chemical Carcinogenesis Research Information System (CCRIS).[36] From the CPDB we selected all chemicals listed under mammary gland in the "Summary Table of Carcinogenic Potency Database by Target Organ."

The CPDB includes 1485 chemicals reported in studies that conformed to a set of 15 criteria.[37] These criteria do not include evaluation of mammary gland tissue for tumors, so many studies are included that did not assess mammary gland carcinogenicity. The CPDB criteria restrict tumor listings to those that the study authors considered treatment-related and/or are statistically significantly increased by treatment. From the IARC Monographs summaries we searched for "mammary" and included only those that increased mammary gland tumors. The IARC, which restricts reviews to studies available in the open scientific literature, does not have quality criteria for studies that are included in the Monograph reviews, although these reviews often describe key limitations of reviewed studies.[17] From the NTP Technical Reports we included all the chemicals from the table "Chemicals Associated with Site-Specific Tumor Induction in Mammary Gland," and we also searched NTP study abstracts and target sites in 2-year studies for "mammary" and included only those chemicals that increased mammary gland tumors. From the NTP 11th ROC we included those chemicals that were returned after a search for "mammary" if they increased mammary tumor incidence. Finally, we included the chemicals from CCRIS selected by the search term "mammary" that had positive results in the "Carcinogenicity Studies" section. According to Technical Resources International, which maintains the CCRIS database for the National Library of Medicine, the database includes studies from primary journals provided by the Chemical Abstracts Service (Columbus, OH) and government reports. The database restricts studies to those where information has been provided on dose, route, durations, species, strain, numbers, and tumor analysis methods. Additional criteria include, for example, the requirement of at least 2 doses with 25 animals per sex per treatment, known chemical purity, and survival of treated animals within 15% of controls.

To facilitate future evaluation of the strength of evidence for mammary gland tumors, we selected the 97 mammary carcinogens with current or past widespread exposure (high production volume, food additives, air pollutants, consumer product chemicals, or >5000 women exposed at work) and recorded full citation information for positive studies in the Mammary Carcinogens Review Database.[31] For 32 of these chemicals we reviewed the experimental details of individual studies, extracting key information from each study into the database. We did not systematically identify and evaluate studies that did not show increased mammary tumors because negative results may be due to inappropriate study design (eg, insufficient pathology, study duration, number of animals, etc), and evaluation of every cancer study conducted on these chemicals was beyond the scope of this effort. In the absence of conflicting information, positive results in a single well-conducted study are generally considered sufficient to identify a chemical as a potential human carcinogen.[17,25,35] Any significant (eg, NTP) studies that were not positive for mammary gland tumors are discussed in the mammary tumor summary. For chemicals that were listed in the CPDB, any citations for studies that did not report increased mammary gland tumors are also included in our database because these studies met certain minimum quality standards determined by the CPDB authors.[37] However, some of these studies may not have included assessment of mammary gland for tumors.

Sources for Carcinogenicity Assessment and Exposure Data

We obtained IARC and U.S. EPA summary weight of evidence determinations of each chemical's carcinogenic potential to humans from the IARC Monograph summaries[33] and the Integrated Risk Information System (IRIS),[38] respectively.

Chemicals produced in the U.S. at >1 million pounds/year in 2002 were identified as high production volume (HPV) chemicals by searching information submitted by companies under the 1986–2002 Toxics Substances Control Act (TSCA) Inventory Update Rule (IUR)[39]; the inventory contains production data for 9000 substances manufactured (or imported) for commercial purposes in amounts of ≥25,000 pounds at a single site.

We classified chemicals as air pollutants if they have been reported in indoor or outdoor air, or may off-gas from consumer products, leading to exposure outside of the workplace.

We obtained summaries of opportunities for exposure and information on current and historical use in consumer products from the following sources: IARC Monographs,[33] NTP Technical Reports,[34] NTP 11th ROC,[35] National Library of Medicine's (NLM) Hazardous Substance Database,[40] U.S. EPA's Source Ranking Database (SRD),[41] NLM's Household Products Database (HPD),[42] the Scorecard Website,[43] Pesticide Action Network Pesticides Database,[44] NLM's ToxNet[45] and PubChem,[46] and *The Merck Index*.[47] If a chemical could not be found in any of the above sources, we used the Google.com search engine to search for the chemical by both name and CAS No. and referenced any of the relevant links provided.

Chemicals identified as food additives in the U.S. were located in the "Everything added to food in the United States" (EAFUS) database developed by the

TABLE 1
Originating Data Sources for Identifying Animal Mammary Carcinogens

Data source	Search strategy	No. of chemicals identified
International Agency for Research on Cancer[33]	Searched all Monographs for "mammary" and included only those that increased mammary tumors	96
U.S. National Toxicology Program[34,35]	Included all chemicals from the table "Chemicals Associated with Site-Specific Tumor Induction in mammary gland"	46
	Used the search term "mammary" in: NTP Study Reports Collection: Abstracts or NTP Study Reports Collection: Target sites in 2-year studies	47
	11th Report on Carcinogens (2004)	61
Carcinogenicity Potency Database[32]	Included all chemicals from the "Summary Table of the Carcinogenic Potency Database by Target Organ" for mammary gland	111
Chemical Carcinogenicity Research Information System[36]	Searched for "mammary" and chose chemicals with any positive results in "Carcinogenicity Studies"	131
Total		216

U.S. Food and Drug Administration (FDA).[48] We identified chemicals expected to have >5000 women exposed occupationally by reviewing the National Occupational Exposure Survey (NOES), which collected information in 1981 to 1983 on types of chemical exposures associated with various job categories in the U.S., and included an estimate of workers in those jobs by gender in 1981 to 1983.[49] Although these data may not reflect current exposure levels and patterns, they are the best currently available and may be useful for identifying cohorts of older women with a history of exposure to mammary carcinogens.

Summaries of findings related to mammary gland tumors were extracted from the NTP 11th ROC,[35] CPDB,[32] IARC,[33] or other sources as referenced; or they were developed based on our review of the original studies.

To study the interpretation of the mammary carcinogen data in governmental and other risk assessment documents, we collected and reviewed information from the following sources: U.S. EPA IRIS,[38] the NIOSH Pocket Guide to Chemical Hazards,[50] and the NIOSH list of Occupational Safety and Health Administration (OSHA)-required medical surveillance for exposed workers.[51] For a subset of 11 chemicals (ethylene oxide, methylene chloride, vinylidene chloride, MX (3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone), and several PAHs and nitro-PAHs) that have been the subject of recent risk assessments, we also reviewed governmental and nongovernmental risk assessments from a wide range of agencies and groups. We specifically searched for documents by the following organizations: California EPA Office of Health Hazard Assessment, Health Canada, IARC, International Program on Chemical Safety (IPCS), World Health Organization, RIVM (Dutch chemical standards agency), Toxicology Excellence for Risk Assessment International Toxicity Estimates of Risk (ITER) database and Peer Consultation documents, and by searching PubMed, ToxLine, the National Library of Medicine, and Google for documents related to "risk assessment" and the CAS number or chemical name.

RESULTS

We identified 216 chemicals that have been associated with increased mammary gland tumors in at least 1 animal study. Table 1 identifies the data sources we accessed to generate this list and indicates the number of chemicals identified from each source. The Mammary Carcinogens Review Database now provides the most comprehensive list of known or potential mammary gland carcinogens.

Table 2 lists all 216 chemicals identified as animal mammary gland carcinogens and indicates the originating data source(s), IARC and U.S. EPA overall assessments of potential carcinogenicity to humans, HPV chemical status in the U.S., and whether the chemical is an FDA-approved food additive or is likely to be an air pollutant, a constituent in consumer products, a contaminant in food, or an occupational exposure to >5000 women, as listed by NIOSH. Of the 216 chemicals on the list, 29 are produced in the U.S. at >1 million pounds/year, 35 are likely pollutants of outdoor (ambient) or indoor (residential) air, 25 have involved occupational exposures to greater than 5000 women, 10 are registered with FDA as food additives, and 73 are or have historically been present in consumer products or as contaminants of food (Table 2). Thus, although these characteristics are not necessarily proxies for general population exposures (eg, a few HPV chemicals are only used in closed manufacturing

TABLE 2
Chemicals Shown to Cause Mammary Gland Tumors in Animal Studies

Chemical name	CAS No.	Originating list*	IARC class†	EPA class‡	HPV chemical§	Air pollutant‖	In consumer products¶	Food additive#	♀ Occup. exposed**
Industrial chemicals (n = 36)									
1,2-Dibromoethane	106-93-4	P,I,N,C	2A	***	•	•			
1,2-Propylene oxide	75-56-9	P,I	2B	B2	•		•	•	•
1,3-Butadiene	106-99-0	P,N,C	2A	****	•	•	•		
1,4-Dioxane	123-91-1	P,I,C	2B	B2	•	•	•		
2,2-Bis(bromomethyl)-1,3-propanediol	3296-90-0	P,I,N,C	2B		•		•		
2,3-Dibromo-1-propanol	96-13-9	I,N,C	2B				•		
2,4-Diaminotoluene	95-80-7	P,N,C	2B				•		
2,4-Dinitrotoluene	121-14-2	P,I,N,C	2B	B2					
2-Chloroacetophenone	532-27-4	N					•		
2-Methylaziridine	75-55-8	N,C	2B				•		
4,4′-Methylene-bis(2-chloroaniline)	101-14-4	P,I,N,C	2A		•		•		
5-Nitroacenaphthene	602-87-9	P,I,N,C	2B						
Acrylamide	79-06-1	P,I,N,C	2A	B2	•	•	•		
Acrylonitrile	107-13-1	P,I,N,C	2B	B1	•		•		•
AF-2 (2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide)	3688-53-7	P,I,C	2B				•		
Benzene	71-43-2	P,N,C	1	A	•	•	•	•	•
Chloroprene	126-99-8	P,I,N,C	2B		•		•		
Ethylene oxide	75-21-8	P,I,N	1		•	•	•	•	•
Glycidol	556-52-5	P,I,N,C	2A						
Hydrazine	302-01-2	I	2B	B2	•	•		•	
Hydrazobenzene	122-66-7	P,N		B2					
Indium phosphide	22398-80-7	N, I	2A						
Nitrobenzene	98-95-3	P,N,C	2B	D	•	•	•		
Nitromethane	75-52-5	P,I,N,C	2B		•	•	•		•
N-Nitroso-di-n-butylamine	924-16-3	N	2B	B2		•	•		
o-Nitrotoluene	88-72-2	N,C			•		•		
o-Aminoazotoluene	97-56-3	N	2B						
o-Toluidine	95-53-4	P,I,N	2A		•	•	•		•
Perfluorooctanoic acid	335-67-1	††					•		
Propane sultone	1120-71-4	P,I,N,C	2B				•		
Styrene	100-42-5	P,I,C	2B		•	•	•	•	•
Toluene diisocyanate mixtures	26471-62-5	P,I,N,C	2B		•		•		
Urethane	51-79-6	N,C	2B				•		•
Vinyl chloride	75-01-4	P,I,N,C	1	A	•		•		•
Vinyl fluoride	75-02-5	P,I,N,C	2A		•		•		
Vinylidene chloride	75-35-4	P,I,C	3	C	•	•	•		
Chlorinated solvents (n = 6)									
1,1-Dichloroethane	75-34-3	N		C			•		
1,2-Dichloroethane	107-06-2	P,I,N,C	2B	B2	•	•	•	•	•
1,2,3-Trichloropropane	96-18-4	P,I,N,C	2A		•				
1,2-Dichloropropane	78-87-5	N,C	3		•		•		

(continued)

TABLE 2
(*continued*)

Chemical name	CAS no.	Originating list*	IARC class†	EPA class‡	HPV chemical§	Air pollutant‖	In consumer products¶	Food additive#	♀ Occup. exposed**
Carbon tetrachloride	56-23-5	P,I,N	2B	B2	•	•	•		•
Methylene chloride	75-09-2	P,I,N,C	2B	B2	•	•	•	•	•
Products of combustion (n = 18)									
1,3-Dinitropyrene	75321-20-9	C	3			•			
1,8-Dinitropyrene	42397-65-9	I,N,C	2B			•			
1-Nitropyrene	5522-43-0	P,I,N,C	2B			•			
2-Aminoanthracene	613-13-8	C				•			
2-Nitrofluorene	607-57-8	I	2B			•			
3-Amino-1-methyl-5h-pyrido[4,3-b] indole	62450-07-1	C	2B				•		
3-Methylcholanthrene	56-49-5	P				•			
4-Nitropyrene	57835-92-4	I,N,C	2B			•			
6-Nitrochrysene	7496-02-8	N	2B			•			
7,12-Dimethylbenz[a]anthracene	57-97-6	C				•			
Benzo[a]pyrene	50-32-8	N ,C	2A	B2		•			
Dibenz[a,h]anthracene	53-70-3	N	2A	B2		•			
Dibenzo[def,p]chrysene	191-30-0	C	2B			•			
IQ	76180-96-6	P,I,N,C	2A				•		
Isoprene	78-79-5	I,N,C	2B		•	•	•		
MeIQ	77094-11-2	I,N,C	2B				•		
PhIP	105650-23-5	I,N,C	2B				•		
Trp-P-2 acetate	72254-58-1	P					•		
Pesticides (n = 10)									
1,2-Dibromo-3-chloropropane	96-12-8	P,I,N,C	2B			•	•		
Atrazine	1912-24-9	P,I,C	3			•	•		
Captafol	2425-06-1	P	2A				•		
Chlordane	12789-03-6	C		B2		•	•		
Clonitralid	1420-04-8	N					•		
Dichlorvos	62-73-7	N,C	2B	B2		•	•		
Fenvalerate	51630-58-1	I	3				•		
Nifurthiazole	3570-75-0	P,I,C	2B						
Simazine	122-34-9	I	3			•	•		
Sulfallate	95-06-7	P,I,N,C	2B				•		
Dyes (n = 18)									
2,4-Diaminoanisole sulfate	39156-41-7	P,N					•		
3,3′-Dichlorobenzidine	91-94-1	P,I,N,C	2B	B2	•		•		
3,3′-Dimethoxybenzidine	119-90-4	N	2B				•		
3,3′-Dimethylbenzidine	119-93-7	N	2B				•		•
4,4′-Methylene-bis(2-methylaniline)	838-88-0	P,I	2B						
4-Aminobiphenyl	92-67-1	P,I,N,C	1			•	•		
5-Nitro-*o*-anisidine	99-59-2	I	3				•		
Amsonic acid	81-11-8	N			•		•		
Benzidine	92-87-5	P,I,N	1	A			•		

(continued)

TABLE 2
(*continued*)

Chemical name	CAS no.	Originating list*	IARC class†	EPA class‡	HPV chemical§	Air pollutant‖	In consumer products¶	Food additive#	♀ Occup. exposed**
C.I. Acid Red 114	6459-94-5	N	2B				•		
C.I. Basic Red 9 monohydrochloride	569-61-9	N,C	2B				•		
C.I. Direct Black 38	1937-37-7	P,I,N,C	2A				•		•
FD&C Violet No. 1	1694-09-3	P,I,C	2B				•	•	
Guinea green B	4680-78-8	I	3				•	•	
HC Yellow no. 3	56932-45-7	C							
Leucomalachite green	129-73-7	N					•		
Malachite green	2437-29-8	N					•		
N,N′-Diacetylbenzidine	613-35-4	I,C	2B						
Radiation and drinking water disinfection (n = 5)									
Magnetic fields		I	3						
MX (3-Chloro-4-(dichloromethyl)-5-hydroxy-2(5h)-furanone)	77439-76-0	P,I,C	2B				•		
Neutrons		I	1						
Radionuclide hydrogen-3		I	1						
X-rays, gamma rays (ionizing radiation)		I	1						•
Pharmaceuticals (n = 47)									
1-(2-Hydroxyethyl)-3-[(5-nitrofurfurylidene) amino]-2-imidazolidinone	5036-03-3	P							
1,2-Dimethyl-5-nitroimidazole	551-92-8	P							
1-[(5-Nitrofurfurylidene)amino]-2-imidazolidinone	555-84-0	P,I,C	2B						
2-Amino-5-(5-nitro-2-furyl)-1,3,4-oxadiazole	3775-55-1	P							
2-Amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole	712-68-5	P,I,C	2B						
2-Amino-5-nitrothiazole	121-66-4	P,I	3				•		
4,4′-Sulfonylbisacetanilide	77-46-3	P							
4-Methyl-1-[(5-nitrofurfurylidene) amino]-2-imidazolidinone	21638-36-8	P							
5-(Morpholinomethyl)-3-[(5-nitrofurfurylidene)-amino]-2-oxazolidinone-l form	3795-88-8	I	2B						
5-Azacytidine	320-67-2	P	2A						
Acronycine	7008-42-6	P,N,C							
Doxorubicin (Adriamycin)	23214-92-8	I,N,C	2A						•
Amsacrine	51264-14-3	I	2B						
anti-(+/-)-trans-7,8,9,10-Tetrahydrobenzo [a]pyrene-7,8-diol-9,10-epoxide	58917-67-2	C							
Bemitradine	88133-11-3	P,C							
Chloroambucil	305-03-3	P,C	1						
Cyclophosphamide	50-18-0	N,C	1						•
Cytembena	21739-91-3	P,N,C							
Dacarbazine	4342-03-4	P,I,N	2B						•
Daunomycin	20830-81-3	I,C	2B						

(continued)

TABLE 2
(*continued*)

Chemical name	CAS no.	Originating list*	IARC class†	EPA class‡	HPV chemical§	Air pollutant‖	In consumer products¶	Food additive#	♀ Occup. exposed**
Dibromomannitol	488-41-5	P							
Furosemide	54-31-9	P,I,N,C	3						•
Griseofulvin	126-07-8	P	2B						
Hexamethylmelamine	531-18-0	P							
Indomethacin	53-86-1	P							
Isoniazid	54-85-3	P	3						
Isonicotinic acid vanillylidenehydrazide	149-17-7	P							
Isophosphamide	3778-73-2	N,C	3						
L-5-Morpholinomethyl-3-[(5-nitrofurfurylidene) amino]-2-oxazolidinone HCl	3031-51-4	P							
Merphalan	531-76-0	I,C	2B						
Metronidazole	443-48-1	P,I,N,C	2B						
Mitomycin-C	50-07-7	C	2B						
Nithiazide	139-94-6	P,I,N,C	3				•		
N,N′-Dimethylnitrosourea	55120-47-3	C							
N-[4-(5-Nitro-2-furyl)-2-thiazolyl]acetamide	531-82-8	P,I,C	2B						
Niridazole	61-57-4	I,C	2B						
Nitrofurantoin	67-20-9	I,C	3						•
Nitrofurazone	59-87-0	P,I,N,C	3				•		
Norlestrin	8015-12-1	P							
Phenacetin	62-44-2	P	2A						•
Phenesterin	3546-10-9	P,N							
Procarbazine hydrochloride	366-70-1	P,I,N,C	2A						
Reserpine	50-55-5	P,I,N,C	3						
SQ 18506	28754-68-9	C							
Thiotepa	52-24-4	I,N,C	1						•
trans-2-[(Dimethylamino)methylimino]-5-[2-(5-nitro-2-furyl)vinyl]-1,3,4-oxadiazole	25962-77-0	I	2B						
Uracil mustard	66-75-1	I,C	2B						
Hormones (n = 17)									
17α-Hydroxyprogesterone caproate	630-56-8	I	2B						
Chlormadinone acetate	302-22-7	I,C	2B						
Conjugated estrogens		I	1				•		•
Diethylstilbestrol	56-53-1	P,I,N,C	1						
Estradiol-17β	50-28-2	I,C	1						•
Estriol	50-27-1	I,C	1						
Estrone	53-16-7	I,C	1				•		
Ethinylestradiol	57-63-6	I,C	1						
Ethynodial diacetate	297-76-7	I,C	2B						
Lynestrenol	52-76-6	I	2B						
Medroxyprogesterone acetate	71-58-9	I,C	2B						
Megestrol acetate	595-33-5	I,C	2B						
Mestranol	72-33-3	I,C	1						

(continued)

TABLE 2
(*continued*)

Chemical name	CAS no.	Originating list*	IARC class†	EPA class‡	HPV chemical§	Air pollutant‖	In consumer products¶	Food additive#	♀ Occup. exposed**
Norethisterone	68-22-4	I,N	2B						
Norethynodrel	68-23-5	I,C	2B						
Progesterone	57-83-0	I,C	2B				•		
Testosterone	58-22-0	I,C	2A						
Natural products (n = 5)									
Bracken fern (and its extracted chemicals)		P,I,C	2B				•		
Carboxymethylnitrosourea	60391-92-6	P							
Methyleugenol	93-15-2	N,C					•	•	•
Ochratoxin A	303-47-9	P,N,C	2B				•		
Wood dust methanol extract		I,N	1						
Research chemicals (n = 15)									
1-Amyl-1-nitrosourea	10589-74-9	P							
2-Acetylaminofluorene	53-96-3	P,C							
2-Aminofluorene	153-78-6	C							
3,2′-Dimethyl-4-aminobiphenyl	13394-86-0	C							
4-(5-Nitro-2-furyl)thiazole	53757-28-1	P,C							
4-Bis(2-hydroxyethyl)amino-2-(5-nitro-2-thienyl) quinazoline	33372-39-3	P							
4-Hydroxyaminoquinoline 1-oxide hydrochloride	1010-61-3	C							
Ethyl methanesulfonate	62-50-0	N	2B						
N-(4-(5-Nitro-2-furyl)-2-thiazolyl) formamide	24554-26-5	C							
N-(9-Oxo-2-fluorenyl)acetamide	3096-50-2	P							
N,N′-Diethyl-N-nitrosourea	49540-32-1	C							
N-N-Butyl-N-Nitrosourea	869-01-2	P,C							
N-Nitroso-N-ethylurea	759-73-9	N,C	2A						
N-Nitroso-N-methylurea	684-93-5	N,C	2A						
Vinyl carbamate epoxide	82617-23-0	C							
Unclassified (likely research chemicals) (n = 39)									
N(6)-(Methylnitroso)adenosine	21928-82-5	P							
1-(2-Hydroxyethyl)-1-nitrosourea	13743-07-2	P							
1-(2-Hydroxyethyl)-nitroso-3-ethylurea	96724-45-7	P,C							
1,3-Dibutyl-1-nitrosourea	56654-52-5	P							
1-Allyl-1-nitrosourea	760-56-5	P,C							
1-Ethylnitroso-3-(2-hydroxyethyl)-urea	96724-44-6	P,C							
1-Ethylnitroso-3-(2-oxopropyl)-urea	110559-84-7	P,C							
2-Hydrazino-4-(5-nitro-2-furyl) thiazole	26049-68-3	P,C							
2-Hydrazino-4-(p-aminophenyl) thiazole	26049-71-8	P							
2-Hydrazino-4-(p-nitrophenyl) thiazole	26049-70-7	P							
2-(2,2-Dimethylhydrazino)-4-(5-nitro-2-furyl) thiazole	26049-69-4	P							
2,2,2- Trifluoro-N-[4-(5-nitro-2-furyl)-2-thiazolyl]acetamide	42011-48-3	P							
2-Methoxy-3-aminodibenzofuran	5834-17-3	P							
3-(5-Nitro-2-furyl)-imidazo(1,2-a) pyridine	75198-31-1	P							
4,6-Diamino-2-(5-nitro-2-furyl)-s-triazine	720-69-4	P							

(continued)

TABLE 2
(*continued*)

Chemical name	CAS no.	Originating list*	IARC class†	EPA class‡	HPV chemical§	Air pollutant‖	In consumer products¶	Food additive#	♀ Occup. exposed**
4,6-Dimethyl-2-(5-nitro-2- furyl) pyrimidine	59-35-8	P							
4-Acetylaminobiphenyl	4075-79-0	P							
4-Aminostilbene	834-24-2	C							
anti-(+/−)-1,2,3,4-Tetrahydrobenzo[c]phenanthrene-3,4-diol-1,2-epoxide		C							
anti-1,2,3,10b-Tetrahydrofluoranthene-2,3-diol 1,10b-oxide	83349-67-1	C							
anti-4,5-Dihydroxy-6,6a-epoxy-4,5,6,6a-tetrahydrobenzo[j]fluoranthene	138857-19-9	C							
anti-9,10-Dihydroxy-11,12-epoxy-9,10,11,12-tetrahydrobenzo[j]fluoranthene	138857-21-3	C							
Azoxyethane	16301-26-1	C							
anti-Benzo[a]chrysene-11,12-diol-13,14-epoxide	132832-26-9	C							
anti-Dibenzo[a,l]pyrene-11,12-dihydrodiol-13,14-epoxide	153926-04-6	C							
Dimethylaminoethylnitrosoethylurea, nitrite salt	142713-78-8	P							
Formic acid 2-(4-methyl-2-thiazolyl)hydrazide	32852-21-4	P							
Methylhydrazine sulfate	302-15-8	C							
N-Hexylnitrosourea	18774-85-1	P,C							
N-(2-Fluorenyl)-2,2,2-trifluoroacetamide	363-17-7	P							
N-(N-methyl-N-nitrosocarbamoyl)-L-ornithine	63642-17-1	P,C							
N,N′-[6-(5- nitro-2-furyl)-s-triazine- 2,4-diyl]bisacetamide	51325-35-0	P							
N-L-Diacetamidofluorene	63019-65-8	P							
N-Ethyl-N′-methyl-N-nitrosourea	72479-23-3	C							
N-Hydroxy-2-(acetylamino)fluorene	53-95-2	C							
N-Hydroxy-N,N′-diacetylbenzidine	71609-22-8	C							
N-Hydroxy-N-formyl-trans-4-aminostilbene	118745-11-2	C							
N-Hydroxy-N-propionyl-trans-4-aminostilbene	118745-12-3	C							
trans-N-Hydroxy-4-acetylaminostilbene	843-23-2	C							

CAS indicates Chemical Abstract Service; IARC, International Agency for Research on Cancer; EPA, Environmental Protection Agency; HPV, high production volume; ♀ Occup. Exposed, females occupationally exposed.

* Identifies the list(s) or data source(s) in which this chemical was identified as causing mammary gland tumors in animals. P is Carcinogenicity Potency Database,[32] I is IARC Monographs,[33] N is National Toxicology Program technical reports or 11th Report on Carcinogens (NTP 2002),[34,35] and C is the National Library of Medicine Chemical Carcinogen Research Information System.[36]

† IARC carcinogenic risk classification. Group 1 – The agent is carcinogenic to humans. Group 2A – The agent is probably carcinogenic to humans. Group 2B – The agent is possibly carcinogenic to humans. Group 3 – The agent is not classifiable as to carcinogenicity in humans. Group 4 – The agent is probably not carcinogenic to humans.[33] The chemicals that have an IARC classification but do not identify IARC as the originating source are chemicals for which our search of IARC abstracts did not identify the word "mammary." For these chemicals, mammary tumors were identified in one of the other data sources. The IARC evaluation and assessment of potential carcinogenicity is based on tumors at all sites.

‡ The U.S. EPA (1986) classification system for the characterization of the overall weight of evidence for carcinogenicity (animal, human, and other supportive data) includes: Group A – Carcinogenic to Humans; Group B – Probably Carcinogenic to Humans; Group C – Possibly Carcinogenic to Humans; Group D – Not Classifiable as to Human Carcinogenicity; and Group E – Evidence of Noncarcinogenicity for Humans.[38]

§ HPV chemicals are those with greater than 1 million pounds produced annually, based on 2002 production volume information submitted to the U.S. EPA.[39]

‖ Chemicals classified as air pollutants are those likely to be found in indoor or outdoor air, including industrial chemicals that may off-gas from consumer products, leading to human exposure.

¶ A positive in this category indicates a chemical is contained in consumer products or traces of the chemical are present in products, including food and water, resulting in possible exposure for the general population. For some chemicals marked as being "in consumer products" consumer product uses have been discontinued.

Listed in the U.S. Food and Drug Administration database, "Everything Added to Food in the United States" (EAFUS).[48]

** More than 5000 women potentially occupationally exposed according to the National Occupational Exposure Survey (NOES) 1981–1983 survey estimates. NOES does not include farm workers.[49]

†† Perfluorooctanoic acid identified as a mammary gland carcinogen in Sibinski (1987).[52]

*** Weight of evidence narrative only. Likely to be carcinogenic to humans.

**** Weight of evidence narrative only. Carcinogenic to humans by inhalation.

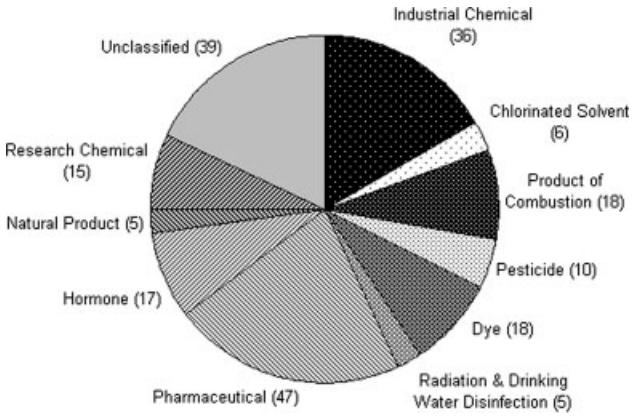

FIGURE 2. Types of chemicals identified as mammary carcinogens. This figure shows the assignment of the 216 mammary gland carcinogens into 11 groups based on chemical use and source. The number of chemicals in each group is provided next to the group name.

systems), there appears to be widespread exposure for many of these chemicals.

Based on information on chemical use and sources, we assigned each chemical to a group. The 216 chemicals included 36 industrial chemicals, 6 chlorinated solvents, 18 products of combustion, 10 pesticides, 18 dyes, 4 types of radiation, 1 drinking water disinfection byproduct, 47 pharmaceuticals, 17 hormones (some of which are pharmaceuticals), 5 natural products, and 54 research chemicals/unclassified chemicals (see Fig. 2). Chemicals that fall into multiple categories were assigned by their most predominant usage. Table 3 provides summaries of exposure potential and mammary tumor findings for the 97 mammary carcinogens with current or past widespread exposure (high production volume, food additives, air pollutants, consumer product chemicals, or >5000 women exposed at work).

We found that risk assessment and regulatory documents have not been developed for many of these chemicals, and those that have typically focus on other target organs, often not discussing the mammary gland tumors or potential for breast cancer. The U.S. EPA uses animal tumor data to develop estimates of the potency of carcinogens so that estimated cancer risks can be calculated in risk assessments used to evaluate regulatory options for various exposure scenarios. The U.S. EPA has developed potency factors for 20 of the 216 chemicals on our list and these factors are based on mammary gland tumors (rather than tumors at other sites) for only 3 of the chemicals (acrylamide 2,4-dinitrotoluene, and 3,3-dichlorobenzidine).[38]

NIOSH has developed standardized reference information on 651 potential workplace chemical hazards and 41 of the 216 mammary carcinogens appear in this guidebook. NIOSH identifies 31 of these as potential occupational carcinogens (based on animal studies) and mammary gland tumors are identified as a target site in animals for only 9 of these.[50] NIOSH is often the primary source of information regarding potential exposure-related health effects for workers, their health and safety officers, and their physicians. Similarly, OSHA requires medical surveillance focused on chemical-specific anticipated adverse health effects for workers exposed to 11 of the chemicals on our list, but none of these requirements include breast cancer screening.[51] Thus, much of the existing toxicological data related to mammary gland tumors is not utilized in chemical risk assessment or regulation.

DISCUSSION

Structural Features of Listed Chemicals

Reviews of chemicals associated with mammary gland tumors in the NTP studies have concluded that certain structural characteristics or chemical classes tend to be associated with mammary gland tumors. These classes include halogenated chemicals and solvents, including components of gasoline; aromatic amino/nitro compounds; dyes; and epoxides or chemicals that form epoxide intermediates.[5,68] This new list of 216 mammary gland carcinogens will facilitate more comprehensive evaluation of structure-activity relations for mammary carcinogens and model development to prioritize chemicals for testing based on their structural features. At the same time, this list points to the diversity of chemical classes and structures associated with mammary gland cancers.

Limitations Related to Identifying the List of Chemicals

This list of chemicals is incomplete in 2 important ways. First, we did not try to identify carcinogenicity studies that were not reported in 1 of the above sources, for example, by exhaustively searching the medical and toxicological literature. This is not likely to be a major limitation, because many of the databases we used as sources included vast literature reviews. A database developed by the U.S. National Cancer Institute[69] compiled references for "compounds that have been tested for carcinogenic activity" and may include studies showing mammary gland tumors for chemicals that we have not listed. Searching and output options for this database were limited, and we were not able to evaluate the listed studies so we did not include chemicals from this source.

The list of 216 chemicals is also incomplete because the carcinogenic potential of most chemicals

TABLE 3
Summary of Exposure and Mammary Gland Tumor Findings for Chemicals With Widespread Exposure*

Chemical name	Opportunities for exposure†	Summary of mammary gland tumors‡
Industrial chemicals		
1,2-Dibromoethane	Detected in ambient air, soil, groundwater, and food. For general population, most important current exposure is through contaminated drinking water due to this chemical's former use as a gasoline additive. Historically, concentrations in ambient air were probably an important source of exposure, especially near automobiles or filling stations. Also used historically and outside of the US as a pesticide.[35]	NTP 11th ROC: When administered by inhalation, 1,2-dibromoethane induced increased incidence of fibroadenomas of the mammary gland in female rats. 1,2-Dibromoethane administered by inhalation induced adenocarcinomas of the mammary gland in female mice.
1,2-Propylene oxide	General population exposure may occur through ingestion of propylene oxide residues in foods from its use as an indirect food additive (gas sterilant). Exposure may also occur by contact with consumer products containing the chemical, especially automotive and paint products that have been found to contain high concentrations of the chemical.[35]	Mixed evidence of mammary gland tumors.
1,3-Butadiene	The primary route of exposure is inhalation. 1,3-Butadiene is a component of vehicle exhaust. Although some food packaging contains residual 1,3-butadiene, the available data indicate that it does not usually migrate to the food. Certain cooking oils, such as rape oil (canola) release 1,3-butadiene when heated.[35]	Three studies found increased levels of mammary tumors, including two NTP Technical Reports.[34,53] NTP 11th ROC: Tumor induction in mice and rats noted in the mammary gland.
1,4-Dioxane	Detected in ambient air (IARC 1999 vol. 71 p. 589).[33] Exposure of the general population to 1,4-dioxane could possibly occur from contact with products containing residues of the compound. According to the Consumer Product Safety Commission (CPSC), consumers may possibly be exposed to residual levels of 1,4-dioxane formed during the manufacture of detergents, shampoos, surfactants, and certain pharmaceuticals. CPSC reported that the presence of 1,4-dioxane, even as a trace contaminant, is cause for concern and the Commission continues to monitor its use in consumer products. Residues may be present in food packaged in 1,4-dioxane-containing materials or on food crops treated with 1,4-dioxane-containing pesticides.[35]	IARC 1999: When administered orally, produced an increased incidence of mammary gland tumors in rats. An NTP study of 1,4-dioxane did not find mammary gland tumors.
2,2-Bis(bromomethyl)-1,3-propanediol	Flame retardant used in polyester resins and polyurethane foams (IARC 2000 vol. 77 p. 455).[33] May enter the environment as dust and through wastewater. It is expected to remain in water for long periods of time. The primary routes of human exposure are inhalation and dermal contact.[35]	An NTP study reported increased mammary tumors.[34] A "negative" study used lower exposure levels.[54] NTP 11th ROC: Two year dietary studies in F344 rats showed significantly increased incidence of neoplasms of the mammary gland in males and females.
2,3-Dibromo-1-propanol (DBP)	The primary routes of human exposure to DBP are inhalation and dermal contact. Shown to be a metabolite and degradation product of tris(2,3-dibromopropyl) phosphate (Tris), a flame retardant that was used in children's sleepwear in the 1970s. DBP was detected in urine of children wearing sleepwear treated with Tris.[35] DBP is also a potential metabolite, impurity, and degradation product of a newer flame retardant [tetrabromobisphenol A bis(2,3-dibromopropyl ether) (CAS 21850-44-2)] which is an HPV chemical produced at >1 – 10 million lbs/year in 2002 and which has been proposed for carcinogenicity testing at NTP.	There is only one study, an NTP study, of this chemical and it used a dermal exposure. DBP caused increased tumors at multiple sites, including the mammary gland (female rats). Tumors (not necessarily mammary) were observed in all animals, even at the lowest doses.
2,4-Diaminotoluene	Potential consumer exposure may occur as a result of the presence of trace contaminants in products that contain 2,4-diaminotoluene-based dyes (e.g. furs, leather, silk, textiles, and wool).[35]	NTP 11th ROC: When administered in the diet, 2,4-diaminotoluene increased the incidence of carcinomas or adenomas of the mammary gland in female rats.
2-Chloroacetophenone	The use of "Chemical Mace" to disable attackers causes direct exposure to 2-chloroacetophenone through eye and skin contact and inhalation.[40]	An NTP study reported an increase in benign mammary gland tumors in female rats.[34]

(*continued*)

TABLE 3
(*continued*)

Chemical name	Opportunities for exposure[†]	Summary of mammary gland tumors[‡]
2-Methylaziridine	Potential consumer exposure could occur as a result of handling products coated with 2-methylaziridine or its derivatives.[35]	NTP 11th ROC: When administered by oral gavage or in the diet, 2-methylaziridine induced mammary adenocarcinomas in female rats.
4,4′-Methylene-bis(2-chloroaniline)	CPSC reported that residual levels of 4,4′-methylene-bis(2-chloroaniline) may be present in final products, such as polyurethane foam and other plastic components. However, data describing actual levels of impurities and the potential for consumer exposure are lacking.[35] Used as a curing agent for roofing and wood sealing in Japan and the Far East (IARC 1993 vol. 57 p. 271).[33]	NTP 11th ROC: When administered in the diet, 4,4′-methylene-bis(2-chloroaniline) induced mammary adenocarcinomas in male rats.
Acrylamide	The general public may be exposed through consumption of certain foods (e.g. french fries). Acrylamide is formed during heating of starch-rich foods to high temperatures. Another source of exposure could be through contaminated drinking water from polyacrylamide flocculants used in water treatment and contact with polyacrylamide-containing consumer products. Used in the manufacture of a number of consumer products, including textiles, contact lenses, building materials, cosmetic and soap preparations, water-based paints, home appliances, automotive parts, food packaging adhesives, paper, and gelatin capsules. Also an environmental contaminant.[35] Tobacco smoke is a substantial non-food source of exposure to acrylamide.[40]	NTP 11th ROC: When administered in the drinking water, acrylamide increased the incidence of mammary adenomas and adenocarcinomas in female rats.
Acrylonitrile	Has been detected rarely and at low levels in ambient air and water (IARC 1999 vol. 71 p. 43).[33] The general population may be exposed through consumer products such as acrylic carpeting, rubber, food containers, and toys or by ingestion of contaminated foods. Exposure in each case, however, is very low because of little migration of the monomer from such products.[35]	NTP 11th ROC: When administered orally, acrylonitrile induced increased incidence of mammary gland carcinomas in rats of both sexes. Inhalation studies demonstrated that acrylonitrile induced mammary tumors in female rats. An NTP study of acrylonitrile in mice did not find mammary gland tumors.
AF-2 (2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide)	A synthetic nitrofuran derivative used as a food preservative in Japan since at least 1965, but it is not used presently (IARC 1983 vol. 30 p. 47).[33] Withdrawn from the market in 1974.[40]	IARC 1983: When administered in the diet, produced benign and malignant mammary tumors in rats of both sexes.
Benzene	Major contributors to benzene emissions into air include: (1) gasoline production, storage, transport, vending and combustion; (2) production of other chemicals from benzene; and (3) indirect production of benzene (e.g. in coke ovens). The last is the major source of benzene emissions into water (IARC 1982 vol. 29 p. 93).[33] Exposure to benzene is highest in areas of heavy motor vehicle traffic and around gasoline filling stations. Consumer products containing benzene include carpet, pesticide products, and adhesive removers. General population also can be exposed to benzene by inhaling air containing tobacco smoke, drinking contaminated water, or eating contaminated food.[35]	Four studies noted mammary tumor increases due to treatment.[33,35,55–57] Some studies that did not show an increase in mammary tumors used only male animals. NTP 11th ROC: When administered orally, benzene caused mammary gland carcinomas and carcinosarcomas in female mice.
Chloroprene	Although few data are available on environmental occurrence, general population exposures are expected to be very low or negligible (IARC 1999 vol. 71 p. 227).[33] Used almost exclusively for the production of neoprene elastomers and latexes, a synthetic rubber used in the production of automotive and mechanical rubber goods, adhesives, caulks, flame-resistant cushioning, construction goods, fabric coatings, sealants for dams or locks in waterways, roof coatings, fiber binding, and footwear (IARC 1999 vol. 71 p. 227).[33,35]	NTP 11th ROC: Inhalation exposure of rats and mice to chloroprene vapors induced increased incidence of neoplasms of the mammary gland in females of both species.

(*continued*)

TABLE 3
(*continued*)

Chemical name	Opportunities for exposure[†]	Summary of mammary gland tumors[‡]
Ethylene oxide	The general population may be exposed to ethylene oxide through use of products that have been sterilized with the compound, such as medical products, foods, clothing, cosmetics, beekeeping equipment, and other products. Ethylene oxide has been detected in tobacco smoke, automobile exhausts, and in some foods and spices.[35]	Two studies have noted mammary tumors.[34,58] Both show higher incidence at the lower dose than the higher dose. One of the "negative" studies only used male rats. NTP 11th ROC: Sites of tumor induction in mice included the mammary gland. One study reported an increased incidence of breast cancer in a cohort of workers who used ethylene oxide as a sterilant.
Hydrazine	Detected at low levels in wastewater (IARC 1999 vol. 71 p. 991).[33] The exposure potential for the general population is low, but it may occur through inhalation of cigarette smoke or ingestion of trace amounts in processed foods.[35] Another possible exposure includes dermal contact with vapors and other products manufactured with hydrazine such as textile dyes, pharmaceuticals, and photography chemicals.[40]	Very limited evidence of mammary gland tumors.
Nitrobenzene	Detected in surface and groundwater (IARC 1996 vol. 65 p. 381).[33] The general public potentially is exposed to nitrobenzene in the environment through inhalation of ambient air, ingestion of water, or dermal contact with products or water containing nitrobenzene. Nitrobenzene is found in soaps and shoe and metal polishes and is used as a preservative in spray paints, constituent of floor polishes, substitute for almond essence, and in the perfume industry.[35,40]	NTP 11th ROC: Exposure to nitrobenzene caused mammary gland tumors in female B6C3F1 mice.
Nitromethane	Exposures may occur from the use of solvents, aeresol propellants and fuels containing nitromethane (IARC 2000 vol. 77 p. 487).[33] Listed as an ingredient in manicuring preparations and rubber adhesives. Nitromethane has been detected in air, surface water, and drinking water. The general population may be exposed by inhalation of nitromethane in motor vehicle exhaust and cigarette smoke.[35]	NTP 11th ROC: In rats, nitromethane caused mammary gland tumors in female F344/N rats but did not cause any increased tumors in Long-Evans rats (exposed to lower levels).
N-Nitroso-di-n-butylamine	N-Nitrosamines, such as N-nitroso-di-n-butylamine, are frequently produced during rubber processing and may be present as contaminants in the final rubber product. Nitrosamines present in pacifiers and baby bottle nipples can migrate from the pacifier or nipple into saliva, which could result in ingestion of nitrosamines.[35] Has been found in cooked fish, pork luncheon meat, the interior of new cars, cigarette smoke, and an aqueous rubber extract.[40] Estimates indicate that air, diet, and smoking contribute to potential human exposure at levels of a few micrograms per day.	NTP 11th ROC: This compound caused mammary carcinomas in female mice.
o-Nitrotoluene	Human exposure to nitrotoluenes can occur during their production and use, although few data are available. Detected in effluents from the manufacture or use of nitrotoluenes and in surface and groundwater (IARC 1996 vol. 65 p. 409).[33] Consumer products that may contain this chemical include: art materials, putty, glazing, wood preservatives and brush cleaners.[41]	An NTP study reported an increase in benign mammary gland tumors in female and male rats.[34]
o-Toluidine hydrochloride	Human exposure has been reported during its use in production of dyestuffs and rubber chemicals. Non-occupational exposure to ortho-toluidine may result from its occurrence in certain foods and from exposure to tobacco smoke (IARC 2000 vol. 77 p. 267).[33] The general population may be exposed to low concentrations in ambient air, tobacco smoke, food, or dermal contact with commercial products.[35]	NTP 11th ROC: When administered in the diet, o-toluidine hydrochloride increased the incidence of mammary gland fibroadenomas and adenomas in female rats.
Perfluorooctanoic acid	Used in non-stick and stain-resistant coatings on rugs, furniture, clothes, cookware, fire-fighting applications, cosmetics, lubricants, paints, and adhesives. Former use in insecticide and herbicide formulations resulted in its direct release to the environment.[40] Widely detected in blood samples in the US.[59]	Two studies demonstrate that PFOA is a multi-site carcinogen. The single study that included females observed mammary gland tumors in female rats.[52]

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Chemical name	Opportunities for exposure[†]	Summary of mammary gland tumors[‡]
Propane sultone	Consumers are potentially exposed to its residues when using detergents, corrosion inhibitors, and other products manufactured from 1,3-propane sultone.[35]	NTP 11th ROC: When administered by gavage, 1,3-propane sultone induced significant increases of mammary adenocarcinomas in female rats.
Styrene	Exposure to the general population occurs at levels of micrograms per day due mainly to inhalation of ambient air and cigarette smoke and intake of food that has been in contact with styrene-containing polymers (polystyrene). Also present in a number of consumer products including carpets, adhesives, hobby and craft supplies, and home maintenance products (IARC 2002 vol. 82 p. 437).[33]	One study[60] reported increased mammary tumors and a number of others, including an NTP study, did not.
Toluene diisocyanate mixtures	Because of the high volatility of toluene diisocyanates, exposure can occur in all phases of its manufacture and use. Household products employing polyurethane varnishes or foam such as furniture, carpet underlay, and bedding may volatize unreacted toluene diisocyanates. FDA has determined that levels of toluene diisocyanates in food, food additives, or food packaging are very low.[35]	NTP 11th ROC: When administered by gavage in corn oil, commercial-grade toluene diisocyanate (analyzed as 85% 2,4-isomer and 15% 2,6-isomer) induced mammary gland fibroadenomas in female rats.
Urethane	Utilized as a solvent for organic materials and co-solvent in the manufacture of pesticides, fumigants, and cosmetics. Found to occur in foods made by a fermentation process, including ale, beer, bread, wine, soy sauce, yogurt, and olives. The general population may be exposed via ingestion of fermented foods and alcoholic beverages.[40]	NTP 11th ROC: When administered in the drinking water, urethane induced mammary carcinomas in mice of both sexes; and mammary tumors in hamsters of both sexes. When injected intraperitoneally, urethane increased incidence of mammary tumors in rats of both sexes. X-irradiation combined with administration of urethane led to the induction of mammary carcinomas in mice. Vinyl carbamate epoxide, a metabolite of urethane, also causes mammary gland tumors.
Vinyl chloride	Used almost exclusively by the plastics industry to produce polyvinyl chloride (PVC), a plastic resin (vinyl) used in many consumer and industrial products. Previously was used as a refrigerant and in aerosol propellants, including hairsprays, but these uses were banned in 1974.[35] The general population may have some limited exposure to vinyl chloride, particularly through direct or indirect contact with polymer products (IARC 1979 vol. 19 p. 377).[33]	NTP 11th ROC: In mice of both sexes, vinyl chloride caused mammary gland tumors. In rats, vinyl chloride caused mammary gland tumors in females. In hamsters, vinyl chloride caused mammary gland tumors in females.
Vinyl fluoride	Used in the production of polyvinylfluoride, which has been used to cover walls, pipes, and electrical equipment, and inside aircraft cabins.[35]	NTP 11th ROC: Female mice showed an increased incidence of mammary gland adenocarcinomas.
Vinylidene chloride	The general population may be exposed via inhalation of ambient air, ingestion of food and drinking water, and dermal contact with consumer products, such as plastic wrap which contains residual monomer.[40] Migration of this chemical into food wrapped in plastic is likely. Detected in wastewater (IARC 1999 vol. 71 p. 1163).[33]	Mammary gland tumors were observed in some studies but did not show dose-response relationships. Vinylidene chloride has structural similarity to other mammary gland carcinogens. An NTP study of vinylidene chloride did not find mammary gland tumors.
Chlorinated solvents		
1,1-Dichloroethane	General population may be exposed via inhalation (for those people living near source areas), ingestion of contaminated drinking water, and via use of consumer products such as paint removers which may contain this compound.[40]	One NTP study reported mammary tumors.[34]
1,2,3-Trichloropropane	Formerly produced for use as a paint and varnish remover and as a cleaning and degreasing agent. Also formerly used as soil fumigant (until 1991). Detected in water, including drinking water, and in soil as a result of its presence as an impurity in a commercial nematocide (IARC 1995 vol. 63 p. 223).[33] The general population may be exposed to low levels of TCP by ingestion of contaminated well water or by inhalation of contaminated air.[35]	NTP 11th ROC: Female rats had increased incidence of tumors in the mammary gland.

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Chemical name	Opportunities for exposure[†]	Summary of mammary gland tumors[‡]
1,2-Dichloroethane	The greatest source of exposure to 1,2-dichloroethane for most of the US population is inhalation of the compound in contaminated air. Dichloroethane has also been detected in food items, possibly due to its use as an extractant in certain food processes.[35] Also present in contaminated drinking water supplies due to its former use as a gasoline additive. Some use in consumer products (adhesives, rug cleaners).[41,43]	NTP 11th ROC: When administered by gavage, 1,2-dichloroethane increased the incidence of mammary gland adenocarcinomas in mice of both sexes and female rats.
1,2-Dichloropropane	Human exposure may occur during domestic use, and due to the presence of low levels in ambient air and in water (IARC 1986 vol. 41 p. 131).[33] Monitoring data indicate that the general population may be exposed to 1,2-dichloropropane via inhalation of ambient air, ingestion of drinking water, and dermal contact with consumer products containing 1,2-dichloropropane.[40]	One NTP study reported mammary tumors.[34]
Carbon tetrachloride	May be used in paint and varnish remover, cleaning and sanitation products, auto products, and hobby/craft products.[41,42] Formerly used as dry cleaning agent, aeresol propellant, pesticide/fumigant and fire extinguisher.[40] Detected at low levels in ambient air and water (IARC 1999 vol. 71 p. 401).[33]	NTP 11th ROC: When administered by subcutaneous injection, carbon tetrachloride induced mammary adenocarcinomas and fibroadenomas in female rats.
Methylene chloride	Widespread exposure occurs during the production and industrial use of methylene chloride and during the use of a variety of consumer products containing it. Consumer products that may contain the chemical include: fabric cleaners, furniture polish, paint strippers, wood sealant and stains, spray paints, adhesives, shoe polish and art supplies.[41] Used until 1989 as a propellant for hair spray. Substantial losses to the environment lead to ubiquitous low-level exposures from ambient air and groundwater (IARC 1999 vol. 71 p. 251).[33,35]	High levels of methylene chloride were associated with benign mammary tumors in rats as well as an increase in the number of mammary tumors per animal. Four of six studies listed in the CPDB reported mammary tumors. NTP 11th ROC: Methylene chloride inhalation also increased the incidence of fibroadenomas of the mammary gland in female rats. There is some evidence of the carcinogenicity of methylene chloride in male rats, as shown by an increased incidence of fibroadenomas of the mammary gland.
Products of combustion		
1-Nitropyrene and other nitro-PAHs	Diesel exhaust is considered the major source of exposure to nitro-PAHs such as 1-nitropyrene. Monitoring data indicate that the general population may be exposed to 1-nitropyrene and other nitro PAHs via inhalation of ambient air, ingestion of food and drinking water, and dermal contact. 1-nitropyrene is one of the most abundant mononitroarenes detected in ambient air.[35]	In studies listed in CPDB and NTP 11th ROC, five of eight studies on 1-nitropyrene reported increased benign and/or malignant mammary tumors from dosing. NTP 11th ROC: When administered by subcutaneous injections, 1-nitropyrene induced mammary tumors (including adenocarcinomas) in female rats. A study in female rats injected intraperitoneally with 1-nitropyrene showed increased mammary tumors; a second intraperitoneal study demonstrated a nonstatistically significant increase in mammary tumors. Mammary gland tumors were also increased following oral administration of 1-nitropyrene to female rats.
Benzo[a]pyrene and other PAHs	Benzo[a]pyrene is found in gasoline and diesel exhaust, cigarette smoke, grilled foods, coal tar and coal tar pitch, soot and smoke, petroleum asphalt, creosote oil, shale oil, and commercial solvents.[35] Exposure occurs primarily through the smoking of tobacco, inhalation of polluted air, and ingestion of charred foods (IARC 1983 vol. 32 p. 211).[33]	NTP 11th ROC: When administered by gavage, benzo[a]pyrene induced mammary tumors in female rats. When administered by intraperitoneal injection, benzo[a]pyrene induced mammary carcinomas in rats.
Isoprene	Formed endogenously in humans. Isoprene is emitted from plants and trees and is widely present in the environment at low concentrations. Sources of anthropogenic releases of isoprene to the atmosphere include ethylene production by petroleum processing, wood pulping, oil fires, wood-burning stoves and fireplaces, other biomass combustion, tobacco smoke, gasoline, and exhaust of turbines and automobiles.[35]	NTP 11th ROC: Inhalation exposure of rats to isoprene vapors induced increased incidence of neoplasms of the mammary gland. Common sites of neoplasm induction by isoprene and butadiene included the mammary gland in mice.

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Chemical name	Opportunities for exposure[†]	Summary of mammary gland tumors[‡]
Pesticides		
1,2-Dibromo-3-chloro propane	Has been detected at low levels in ambient air, water and soil (IARC 1999 vol. 71 p. 479).[33] Widespread exposure of the general population is not likely, since use of the chemical as a soil fumigant was banned in 1985. Exposure of the general population to 1,2-dibromo-3-chloropropane may occur with ingestion of previously contaminated drinking water and food.[35]	NTP 11th ROC: When administered by gavage, 1,2-dibromo-3-chloropropane induced carcinomas of the mammary gland in female rats.
Atrazine	Widely used herbicide. It is found widely, together with its dealkylated degradation products, in rivers, lakes, estuaries, groundwater and reservoirs (IARC 1999 vol. 73 p. 59).[33] The general population may be exposed to atrazine via inhalation of ambient air, ingestion of drinking water, and ingestion of foods that may contain atrazine.[40]	Evidence of increased incidence and/or decreased latency of mammary tumors in female rats. Some evaluations have concluded that tumors result from atrazine-induced hormonal changes in SD rats that are not relevant to humans (IARC 1999 vol. 73 p. 59).[33] However, other evaluations have concluded that inadequate data support this hypothesis.[61]
Captafol	Fungicide that has been widely used since 1961 for the control of fungal diseases in fruits, vegetables, some other plants, and lumber (IARC 1991 vol. 53 p. 353).[33,40] Not currently registered for use as a pesticide in the US.[44]	Evidence of increased incidence of tumors at multiple sites including mammary gland in rats.[62]
Chlordane	Organochlorine insecticide. Used since the 1950s for termite control, on agricultural crops, on lawns, on livestock and for other purposes. Although use of this insecticide has been banned, human exposure is still possible owing to its persistence in the environment and its consequent occurrence in meat, fish and other fat-containing foodstuffs (IARC 2001 vol. 79 p. 411).[33] Still commonly detected in indoor air and house dust in the US.[30]	Very limited evidence of mammary gland tumors.
Clonitralid	Large potential for human exposure resulting from the direct application of the compound for control of sea lamprey larvae in tributaries to the Great Lakes and the widespread application of clonitralid for the control of water snails. The major route of population exposure is presumably dermal contact with or ingestion of treated water or ingestion of contaminated fish (NTP Report No. 91, 1978).[34]	An NTP study of clonitralid found increased mammary adenocarcinomas in male and female rats, however these findings were considered equivocal based on life-table analysis.
Dichlorvos	Household and public health uses represent the main sources of human exposure (IARC 1991 vol. 53 p. 267).[33] The general population may be exposed via inhalation of air and dermal contact when no-pest strips, sprays or flea collars containing this insecticide are used. Exposure could also result from ingestion of food which has been prepared in rooms where dichlorvos is used for insect control.[40]	Most studies done in experimental animals are invalid as cancer bioassays by contemporary standards. One study that used sufficient exposure time and large number of animals,[63] reported an increase in incidence of mammary gland fibroadenomas/adenomas (benign) in one of the two groups of female F344 rats that were fed dichlorvos.[64]
Fenvalerate	Use as a contact insecticide releases the compound directly to the environment in sprays, dusts, concentrates and other routes of application.[40] Consumer products include: pesticide products, landscaping/yard products, and pet care products.[42]	IARC 1991: When administered orally, there was an increased incidence of benign mammary tumors in female rats in one study.
Simazine	Widely used as an herbicide to control grasses and weeds in food crops. Also used for selective control of algae and submerged weeds in ponds. It is approved for algae control in swimming pools, large aquaria, ornamental fish ponds, and fountains.[40] Simazine and its degradation products have been detected at low levels in ambient rural and urban air, rainwater, surface and groundwater and, less frequently, in drinking water samples (IARC 1999 vol. 73 p. 625).[33] Exposure could also occur through consumption of foods containing residues. Simazine residues were not detected in large-scale surveys of food products in Canada and the US (IARC 1991 vol. 53 p. 495).[33]	Similar mechanism of action as atrazine, which shows evidence of increased mammary gland tumors in rats.

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Chemical name	Opportunities for exposure[†]	Summary of mammary gland tumors[‡]
Sulfallate	Sulfallate was used as an herbicide until the early 1990s and is no longer used in the United States. In the past, the general population may have been exposed to sulfallate through ingestion of residues in food crops.[35]	NTP 11th ROC: When administered in the diet, sulfallate induced mammary adenocarcinomas in female rats and mice.
Dyes		
2,4-Diaminoanisole sulfate	An aromatic amine which was used extensively in hair dyes and in the dyeing of furs until the late 1970s (IARC 2001 vol. 79 p. 621).[33] 2,4-diaminoanisole sulfate is a component of cosmetic products. The maximum concentration of the compound in hair-dye preparations is approximately 1.5%.[35]	NTP 11th ROC: When administered in the diet to female rats, 2,4-diaminoanisole sulfate induced mammary adenocarcinomas. An NTP study of 2,4-diaminoanisole sulfate did not find mammary gland tumors.
3,3′-Dichlorobenzidine	For the general population the chance of exposure to 3,3′-dichlorobenzidine and its dichloride salt is probably insignificant. In the past, exposure may have occurred during the use of pressurized spray containers of paints, lacquers, and enamels containing traces of benzidine yellow, an azo dye derived from 3,3′-dichlorobenzidine. Use of 3,3′-dichlorobenzidine to synthesize dyes ended in 1986. However, the greatest chance of exposure is from the improper land disposal of the compounds.[35]	NTP 11th ROC: When administered in the diet, the compound increased the incidence of mammary adenocarcinomas in rats of both sexes.
3,3′-Dimethoxybenzidine	Used as a dye for paper, plastics, rubber, and textiles. Human exposure could occur from trace contaminants in products that are made with 3,3′-dimethoxybenzidine.[35]	NTP 11th ROC: Female rats had increased incidence of cancers of the mammary gland (adenocarcinomas).
3,3′-Dimethylbenzidine	Swimming pool water test kits contain 0.5% to 1.0% 3,3′-dimethylbenzidine. Exposure may occur if the test solutions are emptied into the pool. Residual levels of 3,3′-dimethylbenzidine may be present in dimethylbenzidine-based dyes and pigments and in the final consumer products.[35]	NTP 11th ROC: When given to rats in their drinking water, the dihydrochloride salt of 3,3′-dimethylbenzidine increased the incidence of cancers of the mammary gland (adenocarcinomas) in females.
4-Aminobiphenyl	The potential for exposure to 4-aminobiphenyl is low because it has no commercial uses. It formerly was used as a rubber antioxidant, as a dye intermediate, and in the drug and cosmetic color additive D&C yellow no. 1 (discontinued late 1970s). Mainstream cigarette smoke was reported to contain 4-aminobiphenyl at levels of 2.4 to 4.6 ng per cigarette (unfiltered) and 0.2 to 23 ng per cigarette (filtered), and sidestream smoke to contain up to 140 ng per cigarette.[35]	NTP 11th ROC: When administered to rats by subcutaneous injection, 4-aminobiphenyl caused mammary gland tumors.
5-Nitro-*o*-anisidine	Used as a chemical intermediate in the production of C.I. Pigment Red 23, which is used as a colorant in a wide variety of commodities including printing inks, interior latex paints, lacquers, rubber, plastics, floor coverings, paper coatings, and textiles.	A 1978 study by NTP showed some evidence of mammary gland tumors, but weaknesses in the study limit interpretability. An NTP study of 5-nitro-*o*-anisidine did not find mammary gland tumors.
Amsonic acid	Used in the manufacture of dyes and fluorescent whitening agents or optical brighteners with a range of uses, including in laundry detergents. Potential sources are clothing, especially when moistened by perspiration, packaging materials, some foods, such as fish, and insufficiently rinsed dishes. Little if any direct use of the parent compound by consumers (NTP Report No. 412, 1992).[34]	An NTP study of amsonic acid found a dose-related increase in mammary fibroadenomas which was discounted based on comparison with historical controls.
Benzidine	Limited exposure to the general population since today benzidine may only be produced for captive use in the US and its direct release to the environment is unlikely. Some exposure may occur through past environmental releases since it is moderately persistent.[35,40] Some dyes used to color paper, cloth, leather, food and drinks may contain benzidine as a contaminant or other impurities that can be broken down into benzidine once inside the body. [40]	One study noted slight mammary tumor increase.[32]
C.I. Acid Red 14	Used to dye wool, silk, jute, and leather.[40]	In an NTP study, increased incidence of mammary gland adenocarcinoma in female rats may have been related to chemical administration.[34]

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Chemical name	Opportunities for exposure[†]	Summary of mammary gland tumors[‡]
C.I. Basic Red 9 monohydrochloride	Used to dye textile fibers, in the preparation of pigments for printing inks and in other specialty applications (IARC 1993 vol. 57 p. 215).[33] It is one of three components of commercial magenta, which is used as a dye for coloring textiles (cotton, wool, silks, and acrylics), china clay products, leather, printing inks, and as a filter dye in photography. Its specialty applications include tinting automobile antifreeze solutions and toilet sanitary preparations.[35] Potential consumer exposure could possibly occur through contact with products containing residual dye.[35]	NTP 11th ROC: Increased incidence of mammary gland tumors in female rats may have been related to exposure to the compound.
C.I. Direct Black 38	Azo dyes used on textiles such as cotton, silk, wool, nylon, acetate and leather. Used in aqueous printing inks and as biological stains, plastics, wood stains, wood flour, and hair dyes (NTP Report No. 108, 1978).[34]	NTP 11th ROC: The evidence that dyes metabolized to benzidine are human carcinogens is supported by studies showing that all benzidine-based dyes tested cause cancer in experimental animals. C.I. Direct Black 38 administered in drinking water or in the diet caused malignant mammary gland tumors in mice.
FD & C Violet No. 1	Dye for wool, leather, nylon, anodized aluminum, inks, paper, biological stain, wood stain; color additive for foods, drugs, and cosmetics until 1973.[40]	IARC 1978: After oral administration, produced mammary carcinomas in female rats. It also increased the incidence of benign mammary tumors in female rats following ambient exposure.
Guinea green B	Used to dye wool, silk, leather, paper, and wood. In the past, this color was used as a food, drug and cosmetic dye to color gelatine desserts, frozen desserts, sweets and confections, which did not contain fats and oils, bakery products and cereals, and drug capsules. However, its use as color additive for foods, drugs and cosmetics was forbidden in the US in late 1966, and its use as a food additive was forbidden in Japan in 1967. It is considered to be unsafe for use in food throughout the world. In western Europe, guinea green B can provisionally be used in cosmetics that do not come into contact with mucous membranes; and in Japan, it is used in externally applied cosmetics.[40]	IARC 1978: Following ambient (inhalation) exposure, produced benign mammary tumors in rats.
Malachite green and leucomalachite green	Malachite green and leucomalachite green are widely used as direct dyes for textiles and as antifungal agents in fish hatcheries. They are not approved by the Food and Drug Administration or the Environmental Protection Agency for use on any aquatic species. However, they are relatively inexpensive, readily available, and highly efficacious; therefore, their continued use in some US fisheries is likely. Malachite green and leucomalachite green have been detected in fish (NTP Report No. 527, 2005).[34]	In an NTP study, there was equivocal evidence of increased mammary gland tumors in female rats fed malachite green.[34]
Radiation and drinking water disinfection		
MX (3-chloro-4-(dichloromethyl)-5-hydroxy-2(5h)-furanone)	By-product of drinking water disinfection that has been found at nanogram-per-liter levels in drinking water as a result of chlorination or chloramination (IARC 2004 vol. 84 p. 441).[33] General population may be exposed via treated (chlorinated) drinking water.	Only one study on MX exists and it reports a statistically significant trend of increased mammary tumors with increased dose.[65]
X-rays, gamma rays (ionizing radiation)	The greatest exposure of the general population to X-rays and gamma rays comes from natural terrestrial radiation. The next most significant source is the use of X-rays and radiopharmaceuticals in various diagnostic and therapeutic procedures. Exposures may also occur from the generation of energy by nuclear reactors or accidents at these facilities. Exposures from the atmospheric testing of nuclear weapons have diminished.[35]	Clear evidence of increased mammary gland tumors in animal and human studies.

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TABLE 3
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Chemical name	Opportunities for exposure[†]	Summary of mammary gland tumors[‡]
Pharmaceuticals		
2-Amino-5-nitrothiazole	Synthetic veterinary antiprotozoal agent; general population may be exposed through residues of the chemical in food products (NTP Report No. 53, 1978).[34]	IARC 1983: In one experiment in female rats, 2-amino-5-nitrothiazole increased the incidence of benign mammary tumors. An NTP study of 2-amino-5-nitrothiazole did not find mammary gland tumors.
Doxorubicin	Chemotherapeutic drug used to treat a variety of cancers.[35]	NTP 11th ROC: A single intravenous injection of doxorubicin (adriamycin) induced mammary tumors in female rats.
Cyclophosphamide	Cyclophosphamide has been widely used since the early 1950s in the treatment of malignant lymphoma, multiple myeloma, and cancers of the breast, ovary and lung. It has also been used in the treatment of certain chronic diseases, such as rheumatoid arthritis and chronic glomerulonephritis and other nonmalignant diseases (IARC 1981 vol. 26 p. 165).[33]	NTP 11th ROC: Female rats administered cyclophosphamide by intraperitoneal injection developed benign and malignant mammary gland tumors. Mice administered cyclophosphamide by subcutaneous or intraperitoneal injection developed benign and malignant tumors at various sites, including the mammary gland.
Dacarbazine	Used in cancer therapy (IARC 1981 vol. 26 p. 203).[33]	IARC 1981: Several studies by intraperitoneal injection or diet produced tumors at mammary gland and other organs in rats of both sexes. Following oral or intraperitoneal administration to rats, mammary tumors produced in as little as 18 weeks after initial exposure.
Furosemide	A potent, short-acting sulfonamide diuretic chemically similar to the thiazides, used in a variety of situations ranging from the control of hypertension to the reduction of edema of cardiac, hepatic, or renal origin. It is particularly useful in the management of acute pulmonary edema and may be used in premature infants to promote the diuresis that usually follows birth. The number of prescriptions for furosemide in the United States increased from 16 million in 1973 to 23 million in 1981 (NTP Report No. 356, 1989).[34]	IARC 1990: When administered orally, a small increase in the incidence of mammary gland carcinomas was observed in female mice.
Nithiazide	Humans may be exposed as a result of its use in veterinary medicine (IARC 1983 vol. 31 p. 179).[33] May persist in the tissues and eggs of treated poultry (NTP Report No. 146, 1979).[34]	IARC 1983: When administered in the diet, it increased the incidence of fibroadenomas and cystadenomas of the mammary gland in female rats.
Nitrofurantoin	Used since 1972 in treatment of urinary tract infection (IARC 1990 vol. 50 p. 211).[33]	IARC 1990: When administered orally, female rats demonstrated an increase in the incidence of mammary fibroadenomas. An NTP study of nitrofurantoin did not find mammary gland tumors.
Nitrofurazone	May be present in pet care products. A synthetic furan derivative active against a broad spectrum of bacteria, has been used widely in veterinary and human medicine (NTP Report No. 337, 1988).[34]	IARC 1990: In rats, an increased incidence of mammary fibroadenomas was observed in females when administered orally in two studies.
Phenacetin	Until 1983, phenacetin was used in over-the-counter remedies for pain and fever; however, it no longer is used in drug products in the US. Also, was once used as a stabilizer for hydrogen peroxide in hair-bleaching preparations.[35]	One study reported increased malignant mammary tumors in female rats.[66]
Thiotepa	Used in cancer therapy.[35]	NTP 11th ROC: In rats, intraperitoneal injection of thiotepa caused malignant mammary tumors in females. Malignant mammary gland tumors were significantly increased in the NTP study, however the study authors come to conflicting conclusions as to whether the increase is related to administration of thiotepa. This finding does not appear in the study abstract.
Hormones		
Conjugated estrogens	Used for estrogen replacement therapy and oral contraceptives. Following urinary excretion, can be measured in domestic wastewater and surface water polluted by wastewater.[67] The use of postmenopausal estrogen therapy became common in the United States in the 1960s. By 1967, approximately 13% of the women in the United States 45 to 64 years old used this type of therapy. The number of prescriptions for estrogens, not counting those used for oral contraceptives, increased from approximately 15 million in 1966 to more than 25 million in 1976, when prescriptions declined because of concerns about endometrial cancer, but then increased rapidly to approximately 40 million by 1992. In 2002, more than 100 million prescriptions were filled for brand-name and generic products containing estrogens (either conjugated or esterified) as an active ingredient.[35]	Evidence of increased breast cancer in humans and increased mammary gland tumors in animals.

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Chemical name	Opportunities for exposure[†]	Summary of mammary gland tumors[‡]
Estradiol-17β	Used pharmaceutically as an estrogenic hormone; estrogen replacement therapy; oral contraceptive.[40] Following urinary excretion, can be measured in domestic wastewater and surface water polluted by wastewater.[67]	Evidence of increased breast cancer in humans and increased mammary gland tumors in animals.
Estrone	Unspecified estrogen and estrogenic hormones, which are believed to consist primarily of estrone, have been used in hormonal skin preparations (less than 0.1% to 5%), moisturizing lotions (1% to 5%), wrinkle-smoothing creams, hair conditioners, hair straighteners, shampoos, and grooming aid tonics (less than 0.1%).[35]	IARC 1987: When administered orally, increased incidence of mammary tumors in mice and rats.
Progesterone	Human placental extracts, of which progesterone is believed to be the main constituent, have been used in preparations for cosmetic use (at levels of 0.1% to 1.0%), hair conditioners, shampoos, and grooming aid tonics (<0.1%). Progesterone has been detected in cow's milk, milk products, certain plant species, and meat from animals treated with a progesterone implant. Also used in pharmaceuticals including birth control.[35]	NTP 11th ROC: When progesterone was implanted subcutaneously, mammary carcinomas were induced at a significantly earlier age and at a higher incidence in female mice. Subcutaneous injections of progesterone induced increased incidence of mammary tumors in adult female mice. Female mice injected subcutaneously with progesterone showed decreased latent periods for the induction of mammary tumors by 3-methylcholanthrene. Newborn female rats receiving a subcutaneous injection of progesterone and a subsequent intragastric instillation of 7,12-dimethylbenz[a]anthracene developed increased incidence of mammary adenocarcinomas.
Natural products		
Bracken fern (and its extracted chemicals)	Human exposure to bracken fern and its constituents occurs by direct ingestion of the fronds in some regions of the world, or by ingestion of dairy products from cattle grazing on the fern. In the past, bracken fern has found other end uses such as in bread flour and medicinals (IARC 1986 vol. 40 p. 47).[33] The component ecdysone is being researched as an alternative to pesticides and may be sold as muscle growth supplement.	Some chemicals (ptaquilside and ecdysone) extracted from bracken fern have produced malignant mammary tumors in female rats and mice.
Methyleugenol	A naturally occurring substance, present in many essential oils, including rose, pimento, basil, hyacinth, citronella, anise, nutmeg, mace, cinnamon leaves, pixuri seeds, and laurel fruits and leaves. Methyleugenol is used in commercial products as a flavorant and a fragrance at small concentrations. Used as a flavoring agent in jellies, baked goods, nonalcoholic beverages, chewing gum, candy, pudding, relish, and ice cream.[35]	NTP 11th ROC: In animal studies, methyleugenol given orally to rats induced mammary gland tumors in males.
Ochratoxin A	Naturally occuring mycotoxin; significant food contaminant; widespread occurrence in food and animal feed results in probable human exposure.[35] Human exposure occurs mainly through consumption of contaminated grains, nuts, and pork products (IARC 1993 vol. 56 p. 489).[33]	NTP 11th ROC: Ochratoxin A increased the incidence and multiplicity of fibroadenomas of the mammary gland in female rats

CPDB indicates Carcinogenic Potency Database; CPSC, Consumer Product Safety Commission; IARC, International Agency for Research on Cancer; NTP, National Toxicology Program; ROC, Report on Carcinogens.

* We selected the 97 mammary carcinogens with current or past widespread exposure (high production volume, food additives, air pollutants, consumer product chemicals, or >5000 women exposed at work).

† Text is extracted or closely paraphrased from referenced sources. Additional information is available in the Mammary Carcinogens Database at www.silentspring.org/sciencereview and www.komen.org/environment.

‡ Text is either an extract, closely paraphrased from referenced sources, or it is synthesized by authors of this article based on their reviews. Additional information is available in the online Mammary Carcinogens Database.

is not known, because most substances have not been evaluated. Although the NTP has tested approximately 500 chemicals, and data suggest that other organizations may have tested approximately 500 additional chemicals in similar types of tests,[15] there are 80,000 chemicals registered by the U.S. EPA for commercial use, and of these approximately 3000 are produced at >1 million pounds per year. Although the cancer bioassay is expensive, data on mutagenicity, which can be an indicator of carcinogenic potential of chemicals and can be evaluated in some tests for as little as $5000, is also lacking; the U.S. EPA has mutation data for only 33% of the HPV chemicals.[3] There are also many unpublished studies of carcinogenic potential of chemicals—often these are submitted directly to regulatory agencies by industry sponsors. These studies are difficult to identify and obtain, because they are not indexed anywhere and must typically be obtained by Freedom of Information Act request.

Evaluating Strength of Evidence for Listed Chemicals

Not all chemicals that induce mammary gland tumors in animals are equally carcinogenic or represent a significant risk to humans. The listed chemicals vary in the strength of the evidence that they are likely to be human carcinogens, and each has to be evaluated with respect to potency, dose-response, target sites, tumor incidence and multiplicity, latency, and exposure routes and levels in humans.[2] Likewise, just because chemicals do not cause mammary gland tumors in animals does not mean they will not do so in humans, especially those operating under a hormonal mechanism.

In evaluating the strength of the evidence, it is important to note that, in toxicology, where experimental conditions are well controlled, there is less focus on reproducing positive studies than in epidemiology; and negative studies are not typically counted up and balanced against positive studies. Studies may be negative because of inadequate numbers of animals, animal species and strains, dose levels, length of follow-up, pathology, or inappropriate route of exposure. Another important consideration in assessing strength of evidence in toxicology as opposed to epidemiology is that in toxicology there is no publication bias against negative studies—on the contrary, negative studies are sought after because the objective of toxicology studies is to show how much of a chemical can be tolerated without causing an adverse effect. In the absence of conflicting information, the IARC considers *a single study in 1 species and sex* to provide "sufficient" evidence of carcinogenicity when "malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumor or age at onset, or when there are strong findings of tumors at multiple sites." Otherwise, evidence of carcinogenicity in animals is considered sufficient if there is "an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in 1) ≥2 species of animals or 2) ≥2 independent studies in 1 species performed at different times or in different laboratories or under different protocols," or in "both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices" (eg, a U.S. NTP study).[17] U.S. EPA cancer risk assessment guidelines are similar.[25] Of course, a positive study that is not reproducible (eg, negative results in a study of similar design) would be interpreted cautiously.

Although we did not evaluate the strength of evidence for carcinogenicity for each chemical in our list, 93 of the 132 chemicals that were reviewed by IARC meet the IARC criteria for "sufficient" evidence of carcinogenicity in animals (any tumor sites). This is consistent with our observation that many of the chemicals cause tumors at other sites as well, and cause tumors in both mice and rats. In fact, an analysis by Gold et al.[18] showed that 91% of chemicals from CPDB that were mammary tumorigens in rats also caused tumors at some site in mice, and that 89% of chemicals that caused mammary gland tumors in mice also caused tumors at some site in rats. Taken together with the fact that the chemicals listed in this article are overwhelmingly positive for mutagenic activity (84% with some evidence of mutagenicity, 11% with some evidence of lack of mutagenicity, 5% with no data), it is reasonable to expect from this preliminary assessment that many of them are potential human carcinogens, even at the lower exposure levels expected in humans.

The fundamental question of how well the animal mammary tumor model predicts human breast cancer remains an area of active research and discussion.[21] Ionizing radiation and hormone replacement therapy are the only mammary gland carcinogens with strong evidence of breast cancer in humans, and limited epidemiologic evidence suggests an association for PAHs, solvents, and some others (see companion review by Brody et al.[70] in this issue). However, these limited epidemiologic data are not adequate to answer this question and additional research is needed to develop chemical test methods with demonstrated relevance to human breast cancer.

Findings Related to Interpretation of Mammary Gland Tumors

There are some characteristics of the mammary tumor endpoint that raise challenging issues in inter-

preting study results. Some of the primary issues we identified are:

- Inconsistent interpretation of fibroadenomas (a common benign mammary gland tumor in Fischer rats) including 1) questions regarding progression to malignancy, 2) limited sensitivity due to high background rates, and 3) inappropriate use of nonconcurrent controls;
- Limited understanding of rodent/human differences in hormonal influences on mammary gland tumors, especially the role of prolactin (see Russo and Russo[71] and Harvey[72] for reviews);
- Influence of treatment-related weight loss on dose-response for mammary gland tumors given that mammary tumor rates are higher in heavier animals and high dose groups often experience weight loss; and
- Impact of survival problems and short study duration on sensitivity to mammary gland tumors, because these tumors usually develop late in chronic toxicity studies.

Although discussion of these issues comes up in many risk assessment and toxicology documents, a fruitful source of information on key issues in study interpretation is the NTP expert panel discussion summarized at the beginning of most of the NTP 2-year cancer study reports. The NTP expert panels meet to discuss and approve study conclusions, such as whether the agent showed "clear," "some," "equivocal," or "no" evidence of carcinogenicity, and are typically comprised of toxicologists and pathologists from government, academia, consulting firms, and industry. The strength of each endpoint in each sex and species/strain tested is discussed.

Some specific examples of data interpretation issues are included below to illustrate how these issues ultimately affect the classification of chemicals as to their carcinogenicity.

Inconsistent interpretation of fibroadenomas

Relatively high background rates of fibroadenomas in Fischer rats used at NTP has generated concern that 1) there might be a high rate of false-positive results in which increased fibroadenomas are observed by chance (and there are no other tumor sites), and 2) there might be a high rate of false-negative results because the high background rate obscures the signal. In addition, there are a range of opinions regarding whether fibroadenomas can progress to malignancy in rodents and whether they might be considered predictive of malignant human tumors or only predictive of fibroadenomas (benign tumors that do not progress to malignancy) in humans. Pathology of mammary gland tumors is included in our Mammary Carcinogens Review Database. In the set of 59 chemicals in our database that were evaluated by NTP, only 16 produced fibroadenomas and no other mammary gland tumors in female rats. Of these 16, 10 showed positive or clear evidence of carcinogenicity at some site in mice, 9 showed clear or positive activity at some site in female rats (with another 3 showing some or equivocal evidence in male rats), and only 2 (2-chloroacetophenone and amsonic acid) showed nothing but fibroadenomas. Thus, fibroadenomas (and mammary gland tumors in general) appear to arise when other tumors are also present.

Questions regarding progression to malignancy. Methylene chloride, a commonly used solvent, was evaluated in a 1986 NTP study. The study found significant increases in benign, but not malignant, mammary gland tumors in male and female Fischer rats,[73] and 2 other studies have reported similar findings in Sprague-Dawley rats. NTP guidelines on interpretation of these studies specify that benign, malignant, or combined tumors are all considered evidence of carcinogenicity if the benign tumors can progress to malignancy.[73] In the NTP expert panel review, the Chemical Industry Institute of Toxicology reviewer argued that the proposed rating of "clear" evidence of mammary gland tumors should be changed to "some" evidence, because the tumors were benign. However, the panel voted to maintain the designation of "clear" evidence for benign mammary gland tumors in female rats in this case, because evidence of benign tumors was consistent across multiple studies in different strains and sexes, and the benign tumors were considered to progress to malignancy. Conversely, the IPCS Environmental Criteria Document for methylene chloride dismissed the mammary tumor finding because they believed that an increase in a tumor type that 1) occurs in control animals, 2) does not progress to malignancy, and 3) could be related to changes in prolactin levels is of little significance in the assessment of human hazard.[74] Similar questions have affected interpretation of NTP studies for the widely used human and veterinary pharmaceutical nitrofurazone,[75] and for malachite green and leucomalachite green,[76] which are widely used as antifungal agents in fish hatcheries and have been detected in fish from retail outlets.

High background rates and comparison with historical controls. In a 1992 NTP study, the chemical 4,4′-diamino-2,2′-stilbenedisulfonic acid (amsonic acid) was found to show "no evidence" of carcinogenic activity despite a dose-related increase in benign mammary gland

tumors because the benign tumor rate in controls was low, and the rate in dosed groups was not much higher than in historical controls.[77] Amsonic acid is an industrial chemical used to manufacture whitening agents for detergents and other applications. It is structurally similar to the mammary gland carcinogen diethylstilbestrol (DES), weakly estrogenic in vivo, and associated with reduced testosterone levels and sexual dysfunction in studies of occupationally exposed men.[77–79] Because this NTP study did not mention mammary tumors in its summary documents, the search strategy we used to develop the list of chemicals in this article did not identify amsonic acid as a mammary gland carcinogen. Evidence for mammary gland tumors has also been downgraded based on inappropriate comparison with historical controls for the pesticide dichlorvos[80] and for perfluorooctonoic acid,[81] the chemical used to make stick- and stain-resistant coatings such as Teflon, Stainmaster, Scotchgard, and Gore-Tex.

Rodent/human hormonal differences

Hormonal influences are clearly important in the etiology of human breast cancer, and so differences between animal models and humans in hormonal regulation of mammary gland carcinogenesis are important to consider when selecting animal models for testing hormonally active chemicals.

For example, atrazine, 1 of the most common herbicides in use today, induces mammary gland tumors and premature reproductive aging in female Sprague-Dawley (SD) rats but not F344 rats. These mammary tumors have generally been assumed not to be relevant to humans based on the hypothesis that the premature reproductive aging in SD rats will be associated with elevated estradiol levels, whereas reproductive aging in humans is associated with lower estrogen levels and breast cancer risk.[26] However, data to support this hypothesis (eg, the demonstration of elevated estradiol levels in SD rats after atrazine treatment or during constant estrus) are not available.[61]

Another important difference between certain rat strains and humans is the role of prolactin in mammary gland tumors. It is generally believed that chemicals that cause increased mammary gland tumors by increasing prolactin levels might not be relevant to humans because prolactin has been thought to be unimportant in human breast cancer. The argument that prolactin is not important in human breast cancer has been influential in regulatory processes,[74,82,83] despite the fact that somewhat limited data support this hypothesis.[72] New data derived from the study of dopamine antagonists and breast cancer shows that prolactin plays an important role in human breast cancer and suggests that prolactin-mediated mammary carcinogenesis in rodents may be relevant to humans.[72]

Treatment effects on body weight

Chemical treatment often decreases body weight, and decreased body weight in high-dose groups (associated with chemical toxicity or unpalatability) is likely to inhibit mammary tumors in these animals.

In Gaylor and Kodell,[84] the authors reviewed the NTP study on *p*-nitrobenzoic acid and found that a nonsignificant increasing trend for mammary tumors becomes significant when adjustments are made for body weight effects. They suggested adjusting for body weight effects even if the body weight decrease is less than 10% in the high-dose group. This adjustment has not been consistently employed, which decreases the sensitivity of the studies.

Impact of survival problems

Because mammary gland tumors tend to be late-occurring,[85] studies with short follow-up or high mortality in high-dose groups have reduced sensitivity to mammary gland carcinogens, particularly to nongenotoxic agents.

For example, in the NTP study of toluene diisocyanate mixtures the authors noted that "the survival-adjusted tumor incidences provided a more meaningful comparison than unadjusted overall tumor rates" for combined mammary gland tumors due to the low rate of survival in the high-dose group of female rats beyond the first mammary tumor detection (84 weeks).[5,86]

Findings Related to Consideration of Mammary Tumors in Risk Assessment

We found that risk assessments have not been developed for many of these mammary gland carcinogens and, where they have, often there are controversies in mammary tumor endpoint interpretation. Overall, these factors have resulted in a lack of attention to mammary tumors and to breast cancer in chemical risk assessments that are the basis for environmental policies and regulations. Without complete information regarding the types of health effects that might be associated with chemical exposure in the workplace, for example, physicians and workers have limited ability to make connections between exposures and breast cancer that might otherwise be noticed. As an example of regulatory actions that neglect mammary gland evidence, in its landmark 1997 regulation to lower allowable workplace exposure limits for the mammary gland carcinogen methylene chloride, OSHA proposed that medical surveillance for exposed workers would include breast cancer screening[87]; however, this requirement was dropped in response to objections from Eli Lilly

and others.[88,89] Ethylene oxide is another mammary gland carcinogen with a large number of women potentially exposed because it is used to sterilize medical equipment, foods, and spices. Medical surveillance is required for highly exposed workers, but this regulation does not mention breast cancer or mammary gland tumors and the required surveillance does not include breast cancer screening.[90]

In addition, 2 high-profile risk assessments illustrate the effect of the "missing" mammary gland tumors on public and scientific awareness of the potential role of chemical exposures in breast cancer.

Diesel exhaust is considered the major source of exposure to nitro-PAHs and is also an important source of PAHs, both associated with increased mammary gland tumors in animals and with some human evidence of male and female breast cancer.[70,92–95] Cancer risk from diesel exhaust is a major contributor to overall cancer risk from air pollution—for example the California Air Resources Board has estimated that 70% of cancer risk from toxic air pollution is due to diesel exhaust (the focus is lung cancer so this risk estimate does not include possible breast cancers). Despite the fact that many nitro-PAHs (as well as PAHs) have been consistently shown to cause mammary gland tumors, the IARC 1989 summary report on diesel exhaust,[95] the U.S. EPA IRIS record on diesel exhaust,[38] and U.S. EPA's 669-page Health Assessment Document for Diesel Exhaust[96] do not discuss implications of mammary gland tumors or potential effects on breast cancer.

MX is a mutagenic compound formed during disinfection of drinking water. It has been identified as the major contributor to mutagenicity of chlorinated drinking water.[25,98] Many potentially carcinogenic chemicals are formed during the disinfection process, and many studies have been conducted to describe potential risks, although these have focused on gastrointestinal tract cancers and only a few studies with limited power have evaluated associations with breast cancer.[98] MX is the only identified disinfection by-product (DBP) that has been shown to increase malignant mammary gland tumors in animal studies,[99] but many DBPs have not yet been chemically identified or tested. The U.S. EPA does not mention breast cancer or discuss implications of mammary gland tumors in its most recent regulation pertaining to DBPs; this regulatory risk assessment estimates that between 2% and 17% of all urinary bladder cancers in the U.S. are due to DBPs.[100,101]

The low visibility of possible effects on breast cancer in major documents on health effects of environmental pollutants that may, in fact, affect breast cancer undermines scientific study of breast cancer and public attention to reducing exposure. Perhaps breast cancer researchers, who have been rather skeptical of potential connections to environmental pollutants, would shift perspective if there were routine discussion of breast cancer and mammary gland carcinogens in the risk assessments and other documents where there is evidence that these issues are relevant.

Conclusions and recommendations

To open new avenues of research on breast cancer and environmental pollutants, we compiled a list of 216 animal mammary gland carcinogens. To our knowledge, this is the most comprehensive list of potential breast carcinogens published. We identified and compiled additional information concerning each chemical, including use and exposure, carcinogenicity assessments, mutagenicity, and citations for studies showing mammary gland tumors to facilitate further evaluation by others; these data are publicly available at URL: www.silentspring.org/sciencereview and at URL: www.komen.org/environment. We found the following in our analysis:

- Overall, exposure to mammary gland carcinogens is widespread.
- Nearly all of the chemicals identified as mammary carcinogens were mutagenic and caused tumors in multiple organs and species; these characteristics are generally thought to indicate likely carcinogenicity in humans, even at lower exposure levels.
- Not all chemicals that induce mammary gland tumors in animals are equally carcinogenic or represent equally significant risks to humans, and the strength of evidence needs to be evaluated on a chemical-by-chemical basis.
- Concordance of tumor sites across species is limited, so it is not expected that all these chemicals or that only these chemicals will affect breast cancer in humans.
- Animal models appear to be useful tools for identifying chemicals that may be human breast carcinogens. Mammary gland tumors develop in both mice and rats by chemicals that are often genotoxic and show tumors at other sites. There are inadequate epidemiologic data to evaluate whether mammary gland tumors in animals are predictive of human breast cancer.
- Some characteristics of the animal models lead to uncertainties in interpreting results for mammary gland tumors, and risk assessments used as the basis for regulation often do not mention mammary gland tumors or breast cancer.
- One significant limitation of this list is that most chemicals in use have not been evaluated and

others have not been evaluated adequately for carcinogenic potential.

Our review of literature on mammary gland carcinogens informs research priorities in the areas of epidemiology, toxicology, and risk assessment.

Epidemiology

Mammary carcinogens in animal studies are priorities for follow-up study in humans. To our knowledge, to date only a few epidemiologic studies have provided limited evidence to support an association between breast cancer and exposure to the following mammary gland carcinogens: PAHs, chlorinated solvents, benzene, and possibly ethylene oxide.[70,92–95,102–104] New studies with stronger designs are needed to provide data on the concordance between chemically induced mammary gland tumors in humans and animals. The development of reliable exposure and precancer effect markers will improve the ability of epidemiologic studies to detect associations. Epidemiologic studies of mammary gland carcinogens with widespread exposure and that have never been studied in humans are a priority; human exposure to mixtures of chemicals present special challenges. In addition, better characterizations of women's occupational exposures to these chemicals are needed.

Because methodological difficulties in identifying relations between chemical exposures and breast cancer are significant, we may need to rely on animal models for public health purposes such as developing regulations to limit chemical exposures or reformulating products to reduce use of these chemicals. Many of the chemicals identified are quickly metabolized and not bioaccumulative, so they would be difficult to study in relation to breast cancer, because we would typically not be able to obtain accurate measures of long-term exposure, particularly outside of occupational settings, which are difficult to access for study.

Toxicology

Follow-up activities to this review that would aid in prioritizing these agents for further evaluation or exposure reduction could include: 1) classify listed chemicals according to strength of evidence, considering genotoxicity, hormonal activity, and dose-response relations for tumors; 2) collect additional information on mechanism of action and likelihood of findings being relevant to humans; 3) collect information on typical exposure levels and exposure assessment techniques for these chemicals (biologic and environmental measures).

In addition, this list of animal mammary gland carcinogens provides an opportunity to explore the structural characteristics that are shared among these compounds and that may be responsible for their activity. Structure-activity relation analysis is a necessary part of a chemical screening program, in light of the large number of chemicals in use and the resources required to conduct cancer bioassays.

In the course of this review, we identified the following limitations that are opportunities to improve methods for screening and testing chemicals to identify potential breast carcinogens.

Improvements in standard animal carcinogen bioassays are needed to adapt them to mammary tumors specifically. For example, current protocols do not adequately address increased susceptibility to carcinogens due to early-life exposures, because dosing typically begins in pubertal animals. In addition, hormonal carcinogenic events are often initiated in utero and therefore bioassays beginning with young adult animals typically do not allow these tumors to be initiated. In addition, stopping exposures at 24 months may not allow for the development and manifestation of late-appearing tumors.

Although it is important to identify chemical carcinogens that are genotoxic, as the current protocols are designed to do, it is also important to identify chemicals that act by nongenotoxic mechanisms, for example to promote the growth of cells after they have been initiated by some other carcinogen. The powerful role of endogenous hormones in promoting breast tumor development suggests that environmental chemicals that act as promotors could play an important role in breast cancer. Assays to look for tumor-promoting activity involve treating with a single dose of an initiator and then following with the promoter.

Risk assessment methodologies that capture risks from chemicals that increase mammary gland susceptibility to carcinogenesis by other agents or that act as tumor promoters are needed.

Further evaluation of the mammary tumor endpoint in the cancer bioassay would inform decisions regarding choice of animal model and interpretation in risk assessment and regulatory documents. NTP is currently considering modifying protocols and animal models for the cancer bioassays,[21,105] and it may be fruitful to consider this question with the specific purpose of identifying models that will be effective at screening for potential human breast carcinogens. For genotoxic carcinogens, perhaps the current animal models are adequate, although use of the findings in risk assessment remains an issue. However, for chemicals with hormonally mediated mechanisms, the current models will not necessarily produce relevant results.

Screening of chemicals in the EPA's planned endocrine disruptor testing program[106] will identify hor-

monal activities and mechanisms, allowing animal models to be chosen that are most similar to humans for that mechanism of action.

If methods for identifying potential carcinogens were more efficient, a higher proportion of chemicals in use could be evaluated. At more than $2 million per test, the animal bioassay is an expensive screening tool. Although substantial development and validation are needed, in vitro and short-term in vivo assays could be useful for screening chemicals to prioritize a subset for long-term testing in animals. Research to develop effective screens is a priority. Genomics techniques have demonstrated promise for grouping chemicals according to mechanism of action. However, efforts to develop genomic methods for chemicals testing are currently focused on organs such as the liver and lung, not the mammary gland. Research to characterize changes in gene and protein expression associated with mammary gland carcinogenesis and to develop and validate screening tools based on these findings is a priority. Advances in understanding genetic and epigenetic mechanisms associated with the etiology of breast cancer in humans and appropriate animal models will be required before these technologies can be validated, so a significant investment in resources will be required to make progress in this area. These types of assays can be targeted to identifying relevant effects of endocrine disrupting chemicals as well as classical carcinogens.

Risk Assessment and Regulatory Policy

Our analysis shows that valuable information from cancer bioassays is not well utilized in risk assessment and regulatory processes. Given the substantial resources required to develop toxicological data, this observation leads us to look for ways to strengthen the current practice of chemicals risk assessment and regulation as potentially cost-effective tools for breast cancer prevention.

The current process of developing acceptable practice in the field of risk assessment is highly influenced by industry efforts to minimize restrictions on the chemicals they produce.[29,107] Other interest groups could be effective in advocating for different agendas, including advocacy for better models for identifying potential breast carcinogens, more chemicals to be tested, clearer guidance on interpretation of test results, clearer inclusion of breast cancer in risk communication and risk assessment documents related to mammary gland carcinogens, inclusion of all mammary gland carcinogens in quantitative risk assessments through development of potency estimates, requirements to include mammography in screening programs for women exposed to these chemicals at work, and national exposure monitoring to better characterize population-level exposure patterns.

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