Correlations between Chemically Related Site-specific Carcinogenic Effects in Long-Term Studies in Rats and Mice

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We examined a database of 379 long-term carcinogenicity studies in rats and mice to evaluate sex and species correlations in site-specific carcinogenic responses. Within a species, most target sites showed a strong correlation between males and females. For example, chemicals producing forestomach or liver tumors in males were likely to produce these same types of tumors in females. There was also a significant correlation between species for certain site-specific carcinogenic effects, most notably tumors of the forestomach, liver, and thyroid gland. In contrast, adrenal pheochromocytoma, preputial/clitoral gland neoplasms, and lung tumors showed no significant interspecies correlation. Many chemicals produced a syndrome of carcinogenic effects involving tumors of the skin, Zymbal gland, preputial/clitoral gland, mammary gland, and/or oral cavity. Regarding different target sites, there appeared to be a correlation between thyroid and liver tumors both within and between species. Further, all chemicals producing mesotheliomas in male rats also produced mammary gland neoplasms in female rats. In contrast, kidney and urinary bladder tumors showed no significant association with any other tumor type in rats or mice. If a chemical produced a site-specific carcinogenic effect in female rats or mice, there was approximately a 65% probability that the chemical would also be carcinogenic at that same site in males. The interspecies correlation was somewhat lower: approximately 36% of the site-specific carcinogenic effects ob-served in one species (rats or mice) were also observed in the other species. The high correlation between males and females suggests that in some instances it may be appropriate to consider a reduced protocol such as male rats and female mice. This would result in substantial cost savings, and an examination of NCI/NTP studies suggests that while there will be some sensitivity loss associated with this approach, the rodent carcinogens not detected by this reduced protocol are not those most likely to pose a carcinogenic threat to humans. Nevertheless, the decision of whether to use a reduced protocol is best made on a case-by-case basis. **Key words:** interspecies correlation; laboratory animal studies; National Toxicology Program; rodent carcinogenicity; site-specific neoplasms. *Environ Health Perspect 101(1): 50–54*

The National Cancer Institute (NCI) and the National Toxicology Program (NTP) have designed, carried out, and evaluated more than 400 long-term carcinogenicity studies in laboratory rodents (*1–3*). The purpose of these studies is to identify chemicals that may pose a carcinogenic hazard to humans. The results of these studies have been presented in a series of technical reports and in the scientific literature. These data are used by the international scientific community and by various governmental agencies in making regulatory decisions affecting public health.

The focus of the NCI/NTP studies is the evaluation and interpretation of site-specific carcinogenic effects (*4*) . A recent publication (*2*) presented a tabular summary of site-specific carcinogenicity results for 379 NCI/NTP studies. The purpose of this paper is to investigate correlations in chemically related site-specific carcinogenic responses in this database both within and between species for a variety of different target sites.

Other investigators have considered certain aspects of these associations. For example, Gold et al. (*5,6*) investigated the predictive value of site-specific carcinogenic responses for chemicals in the Carcinogenic Potency Database. Their evaluation differed from ours in that their site-specific analyses involved primarily the same target site in the other species, and the evaluation used data from a variety of sources and thus included studies that did not employ the standardized protocol used by the NCI/NTP.

The primary objective of our investigation is to identify associations between site-specific carcinogenic effects that may increase our understanding of the value and limitations of long-term rodent studies. The implication of these associations on the possible use of a reduced protocol for rodent carcinogenicity evaluation is also discussed.

Methods

The carcinogenicity database used in our analysis consisted of the 379 long-term NCI/NTP studies in rats and/or mice considered by Huff et al. (*2*). The site-specific carcinogenic effects observed in each sex–species group were evaluated for possible associations. The specific target organs used in our evaluation were the 13 most frequent sites of carcinogenicity in these studies (Table 1). Overall, 89% of the rat carcinogens and 91% of the mouse carcinogens in the NCI/NTP database produced carcinogenic effects in at least one of these sites.

Initially, experimental outcomes were divided into three categories: positive, negative, and equivocal. To simplify the analysis, equivocal outcomes were subsequently combined with negative results, because in our judgment chemicals producing equivocal effects are closer to being negative than positive (*7*). However, alternative analyses (results not shown) in which equivocal responses were considered positive or were excluded altogether produced similar results to those reported in this paper.

We considered several types of associations: first, for each target site, we evaluated the correlation in carcinogenic response between males and females within a species for those studies with adequate experiments in both sexes. Second, we evaluated correlations between species for a given target site for those 313 studies with experiments adequate for evaluating carcinogenicity in all four sex–species groups. In these analyses, a species was considered positive if a carcinogenic response was observed in males, in females, or in both sexes. Finally, we evaluated correlations between different target sites both within and between species. Our analyses included noncarcinogens as well as carcinogens.

The strengths of the associations were assessed by Fisher's exact test. Because the analyses involved a large number of comparisons, $p<0.01$ (rather than $p<0.05$) associations were considered significant. This reduces the likelihood of false positive outcomes.

Results

Within a species, most target sites showed a significant correlation between males and females with respect to site-specific carcinogenic responses. Table 2 summarizes the most striking of these associations for

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Table 1. Site-specific carcinogenic effects observed in 379 NTP studies

Site of carcinogenicity	No. of studies with carcinogenic effects		
	Rats	Mice	Rats or mice
Liver	44	86	104
Lung	9	23	30
Hematopoietic system	17	15	29
Kidney (tubular cell)	24	4	27
Mammary gland	22	9	27
Forestomach	15	17	23
Thyroid gland (follicular cell)	16	9	18
Zymbal gland	18	2	18
Urinary bladder	14	4	16
Skin	15	3	15
Clitoral/preputial gland	11	3	14
Circulatory system	4	11	13
Adrenal gland (pheochromocytoma)	5	6	11

Table 2. Sites showing significant ($p<0.0001$) correlation between males and females for chemically related carcinogenicity

Site of carcinogenicity	Carcinogenicity outcome (male/female)			
	+/+	+/–	–/+	–/–
Rats				
Liver	26	11	5	307
Zymbal gland	13	3	2	331
Forestomach	11	4	0	334
Thyroid (follicular cell)	10	3	3	333
Urinary bladder	6	4	4	335
Skin	6	8	1	334
Clitoral/preputial gland	5	1	5	338
Lung	3	2	4	340
Mice				
Liver	47	11	28	253
Lung	16	2	4	317
Forestomach	14	1	1	323
Thyroid (follicular cell)	5	1	3	330
Circulatory system	6	2	3	328
Adrenal medulla	3	2	1	333

Table 3. Interspecies correlation in carcinogenic response for selected target sites

Site of carcinogenicity	Carcinogenicity outcome (rat/mouse)			
	+/+	+/–	–/+	–/–
Significant ($p<0.001$) correlation				
Liver	25	8	53	227
Forestomach	8	6	7	292
Thyroid gland	7	9	2	295
Mammary gland	4	14	3	292
All sites[a]	82	40	40	151
No significant correlation				
Lung	2	5	16	270
Adrenal medulla	0	4	4	305
Preputial/clitoral gland	0	7	3	303

[a]Taken from Huff et al. (*2*).

the 349 rat studies and the 339 mouse studies with adequate experiments for both sexes.

The greatest consistency was found for the forestomach. For example, in rats, all 11 studies showing forestomach carcinogenicity in female rats also showed these effects in males rats (Table 2). Similarly, in mice, 14 of the 15 studies showing carcinogenic forestomach effects in one sex also showed similar effects in the other sex (Table 2). Other sites showing a strong consistency between males and females include liver (rats and mice), Zymbal gland (rats), and lung (mice). In contrast, mammary gland tumors showed relatively low association between males and females because they were induced almost exclusively in females. Also, there were far more carcinogens that produced kidney tumors in male rats than in female rats.

There was also a strong correlation between species for certain site-specific carcinogenic effects. For example, a chemical carcinogenic to the liver of male and/or female rats was four times more likely to be a mouse liver carcinogen than was a chemical not carcinogenic to rat liver (76% = 25/33 versus 19% = 53/280; see Table 3). In analogous comparisons, the corresponding probabilities for forestomach, thyroid, and mammary gland tumors were 57% versus 2%, 44% versus 1%, and 22% versus 1%, respectively (Table 3). All of these differences are highly significant ($p<0.001$).

Equally interesting were the sites showing no significant correlation between species. For example, there were no chemicals in the database that produced adrenal pheochromocytoma or preputial/clitoral gland tumors in both rats and mice (Table 3). The lung was another site showing no significant interspecies correlation in chemically related carcinogenicity: only 2 of the 23 chemicals producing lung tumors showed these effects in both rats and mice (Table 3). If all target sites are considered collectively, the overall interspecies concordance in carcinogenic response is 74% (233/313; see Table 3). This interspecies association is consistent with other published estimates (*5,8*).

Within a sex–species group, certain target sites tended to show carcinogenic effects for the same chemicals. For example, in rats, tumors of the skin, Zymbal gland, preputial/clitoral gland, and (to a lesser extent) mammary gland were intercorrelated (Table 4). Eight chemicals (C.I. acid red 114, C.I. direct blue 15, 3,3′-dimethylbenzidine dihydrochloride, 3,3′ dimethylbenzidine dihydrochloride, 2,4-diaminoanisole sulfate, glycidol, 5-nitroacenaphthene, and 5-nitro-*o*-anisidine) produced carcinogenic effects at 4/4 or 3/4 of these sites, and 8 other chemicals [3-amino-9-ethylcarbazole HCl, benzene, C.I. basic red 9, 2,4-dinitrotoluene, 3,3′-dimethoxybenzidine-4,4′-diisocynate, hydrazobenzene, nithiazide, and tris(aziridinyl)-phosphine sulfide] produced effects at 2/4 of these sites.

Two other target sites that showed an association both within and across species were liver and thyroid gland. The likelihood of a chemical being a rodent liver carcinogen was much higher for those chemicals that were thyroid follicular cell carcinogens than for those chemicals that were not (Table 5). For example, of the 18 chemicals showing thyroid carcinogenicity

Table 4. Significant ($p<0.01$) correlation in chemically related carcinogenic effects for skin, Zymbal gland, preputial/clitoral gland, and mammary gland tumors in rats

	Carcinogenicity outcome			
Sites of carcinogenicity	+/+	+/–	–/+	–/–
Skin/Zymbal gland	12	3	6	328
Skin/preputial-clitoral gland	7	8	4	330
Skin/mammary gland	5	10	17	317
Zymbal/preputial-clitoral gland	8	10	3	328
Zymbal/mammary gland	5	13	17	314
Preputial/clitoral/mammary gland	4	7	18	320

Table 5. Correlation in chemically related carcinogenic effects for liver neoplasms and thyroid gland follicular cell tumors in rats and mice

	Carcinogenicity outcome			
Sites of carcinogenicity	+/+	+/–	–/+	–/–
Rat liver/rat thyroid	6	36	10	297
Rat liver/mouse thyroid	5	28	4	276
Mouse liver/rat thyroid	10	68	6	229
Mouse liver/mouse thyroid	7	79	2	251
Rodent liver/rodent thyroid	11	75	7	220

All associations are significant at the $p<0.01$ level. Rodent = rat or mouse.

Table 6. Other significant ($p<0.001$) correlations between sites in chemically related carcinogenicity

	Carcinogenicity outcome			
Sites of carcinogenicity	+/+	+/–	–/+	–/–
Rat liver/rat Zymbal gland	9	33	9	298
Mouse liver/mouse adrenal medulla	6	80	0	253
Mouse lung/mouse hematopoietic	6	16	8	309
Mouse lung/mouse mammary gland	7	15	2	315
Mouse lung/mouse forestomach	7	15	9	308
Mouse lung/rat mammary gland	7	11	11	284

in rats or mice, 61% (11/18) also produced liver tumors in one or both species. In contrast, for those chemicals not producing thyroid follicular cell tumors, only 25% (75/295) produced rodent liver tumors. This association between liver and thyroid neoplasms has been previously noted (*9*).

There were relatively few other notable correlations between different sites of carcinogenicity, and the most significant of these are summarized in Table 6. Chemically related lung tumors in mice were associated with forestomach and hematopoietic system tumors in mice and with mammary gland tumors in both rats and mice. All six chemicals producing adrenal pheochromocytomas in mice were also mouse liver carcinogens. Liver and Zymbal gland tumors in rats were also correlated.

Kidney and urinary bladder tumors in rats showed no significant association with any other tumor type in rats or mice. Circulatory system tumors in mice did not show strong associations with other tumor types. Interestingly, there were no significant negative correlations in chemically related site-specific carcinogenic responses in the database. That is, there were no target sites for which chemicals producing carcinogenic effects at that site were significantly less likely to produce carcinogenic effects at another site.

Although mesotheliomas were not part of our primary analysis because of the relatively low frequency of carcinogenic effects, it is noteworthy that all six chemicals producing mesothelioma in male rats (cytembena, 1,2-dibromoethane, 3,3'-dimeoxybenzidine dihydrochloride, 3,3'-dimethylbenzidine dihydrochloride, glycidol, and *O*-toluidine hydrochloride) also produced mammary gland tumors in female rats. This association is highly significant ($p<0.0001$).

Another tumor site that was not part of our primary analysis was oral cavity, which showed chemically related neoplastic effects for eight chemicals in rats (none in mice). These tumors are strongly associated with the skin–Zymbal gland–clitoral/preputial gland–mammary gland "syndrome" noted in Table 4: 6/8 chemicals producing oral cavity tumors in rats also produced 2 or more of the other tumors in the syndrome.

Approximately 10% (32/313) of the chemicals adequately evaluated in all four sex–species groups produced single site, single sex–species carcinogenic effects. The organs most often involved were liver (five chemicals for female mice; four for male mice) and kidney (four for male rats). Approximately 58% of the carcinogens in the NTP database are positive in *Salmonella*, compared to 30% of the noncarcinogens (*10*). Gold et al. (*11*) found similar results for chemicals in the Carcinogenic Potency Database. Both investigators (*10,11*) reported that multisite carcinogenicity was associated with *Salmonella* mutagenicity, a finding consistent with our own evaluation. For example, consider the chemicals that produced the multisite syndrome of carcinogenic effects noted in Table 4. Of the 16 chemicals showing site-specific effects in at least 2 of the 4 target sites (skin, Zymbal gland, clitoral/preputial gland, and mammary gland) all but 2 (benzene and C.I. direct blue 15) were positive in *Salmonella*. Similarly, all six chemicals producing mesotheliomas in male rats and mammary gland tumors in female rats were positive in *Salmonella*.

In contrast, chemicals producing kidney tumors (which were not associated with other tumor types) tended to be nonmutagens. Of the 25 chemicals producing male rat kidney tumors, only 28% (7/25) were mutagenic in *Salmonella*. Further, only 31% (4/13) of the chemicals noted above with single sex–species liver or kidney tumor effects were mutagenic in *Salmonella*. These percentages are similar to those observed for the noncarcinogens in the database.

Among the liver carcinogens in the database, 70% (16/23) of the chemicals that produced these neoplasms in both species were mutagenic in *Salmonella* compared to only 30% (7/23) for those chemicals whose only carcinogenic effect was liver tumors in mice (*2,12*). This difference in *Salmonella* mutagenicity (70% versus 30%) is statistically significant ($p<0.05$). One possible explanation for this difference is that a relatively high proportion of mouse-liver-only carcinogens are chlorinated compounds, which tend to be nonmutagenic (*5,11*).

Our evaluation also permits a comparison of the male–female correlation with the interspecies association in site-specific carcinogenicity. This evaluation is summarized in Table 7. Although the interspecies correlation varies for each site of carcinogenicity, if the 13 major target sites are considered collectively, the overall probability is 35% (61/173) that a site-specific carcinogenic effect in rats will also be produced by that chemical in mice at the same site (Table 7). Similarly, 37% (61/167) of the site-specific carcinogenic effects in mice are also produced by the same chemical in rats (Table 7).

Table 7. Correlations in site-specific carcinogenicity: proportion of chemicals carcinogenic in the first sex–species group that are also carcinogenic at that site in the second sex–species group

Site of carcinogenicity	Female rats/ male rats	Female mice/ male mice	Rats/mice	Mice/rats
Liver	26/32	47/75	25/33	25/78
Lung	3/7	16/20	2/7	2/18
Hematopoietic system	5/9	6/12	3/14	3/11
Kidney (tubular cell)	6/7	1/1	3/21	3/4
Mammary gland	3/22	0/9	4/18	4/7
Forestomach	11/11	14/15	8/14	8/15
Thyroid gland	10/13	5/8	7/16	7/9
Zymbal gland	13/15	1/2	2/12	2/2
Urinary bladder	6/10	2/2	2/12	2/3
Skin	6/7	2/2	3/11	3/3
Clitoral/preputial gland	5/10	0/0	0/7	0/3
Circulatory system	2/2	6/9	2/4	2/10
Adrenal medulla	1/1	3/4	0/4	0/4
Total	97/146 (66%)	103/159 (65%)	61/173 (35%)	61/167 (37%)

Table 8. Rodent carcinogens not detected by a reduced protocol of male rats and female mice

Chemical	Target site
Aldrin	Liver (MM)
Allyl glycidol ether	Nasal cavity (MM)
3-Amino-4-ethoxyacetanilide	Thyroid gland (MM)
Chlorinated paraffins (C23, 43% chlorine)	Hematopoietic system (MM)
C.I. acid orange 3	Kidney (FR)
C.I. vat yellow 4	Hematopoietic system (MM)
Daminozide	Uterus (FR)
2,4-Diaminophenol	Kidney (MM)
Dicofol	Liver (MM)
Nithiazide	Mammary gland/skin (FR)
	Liver (MM)
3-Nitro-*p*-acetophenetide	Liver (MM)
Phenylbutazone	Kidney (FR)
	Liver (MM)
Piperonyl sulfoxide	Liver (MM)
p-Quinone dioxime	Urinary bladder (FR)
Trimethylthiourea	Thyroid gland (FR)

FR, female rats; MM, male mice.

For these same target sites, 66% (97/146) of the site-specific carcinogenic effects observed in female rats were also observed in male rats (Table 7). For mice, 65% (103/159) of the site-specific effects observed in female mice also occurred in males. Thus, the agreement between sexes within a species is considerably higher than the corresponding agreement between species.

Discussion

When evaluating associations in site-specific carcinogenic responses, we considered all experimental outcomes, negative as well as positive. For example, there were 61 chemicals that produced liver carcinogenicity in a single species and 25 that produced a liver tumor response in both rats and mice (Table 3). However, this information alone is insufficient to evaluate interspecies correlation in liver tumor carcinogenicity. If there is no interspecies correlation, the likelihood of observing a mouse liver carcinogen should be the same regardless of whether a chemical is a rat liver carcinogen. Thus, had there been only 17 chemicals not carcinogenic to the liver of rats or mice, then the proportion of mouse liver carcinogens would have been 76% (25/33) for rat liver carcinogens and 76% (53/70) for chemicals not carcinogenic to rat liver, indicating no association. However, the actual database contained 227, not 17, chemicals not carcinogenic to the liver of either species (Table 3). Thus, only 19% of the rat liver noncarcinogens were mouse liver carcinogens, and this difference in response (76% versus 19%) implies a strong association, as noted above.

Our evaluation revealed a number of target sites showing significant associations in chemically related carcinogenic responses between species. However, such agreement was far from complete, and the overall probability that a chemical carcinogenic at a particular site in rats will be carcinogenic at the same site in mice (and vice versa) is approximately 36%.

Consideration of different target sites produced similar results. For example, despite the significant ($p<0.01$) correlation between chemically induced liver and thyroid tumors, the vast majority of liver carcinogens (in either species) did not produce thyroid tumors. Similarly, many chemicals produced thyroid tumors without increasing the incidence of liver neoplasms (see Table 5).

There was much better agreement between sexes within a species, and this strong correlation in carcinogenic response between males and females has been noted previously (*3,5,8*). However, these earlier analyses were based on overall carcinogenicity rather than on site-specific effects. Our evaluation shows that this same strong correlation also holds for site-specific carcinogenicity.

These results may have implications for the experimental design of long-term rodent studies. Some investigators have noted that from the standpoint of detecting carcinogenic effects, relatively little sensitivity would be lost by restricting the study to two rather than four sex–species groups (*5,8*). Because the male–female correlation in carcinogenic response is much stronger than the interspecies correlation, a reduced protocol of one sex of each species would be more sensitive for detecting rodent carcinogenicity than using both sexes of either species. The best choice for a reduced protocol may be male rats and female mice (*8*).

For example, of the 162 NCI/NTP chemicals adequately evaluated in all four sex–species groups and found to be carcinogenic in at least one group (see Table 3), only 15 (9%) would not have been detected as rodent carcinogens in a reduced protocol of male rats and female mice. These 15 chemicals, listed in Table 8, generally produce single-site, single sex–species carcinogenic effects. Moreover, the toxicities of these chemicals as measured by the maximum tolerated dose (MTD; *13*) are somewhat lower on average than those of the other carcinogens in the database. More than half of the chemicals (8/15) are negative in the *Salmonella* assay. None are listed as "reasonably anticipated to be" human carcinogens in the NTP Sixth Annual Report on Carcinogens (*14*) or as being "possible" or "probable" human carcinogens by the International Agency for Research on Cancer (IARC). Thus, it appears that a reduced protocol would not miss many of the carcinogens likely to be of public health significance.

However, reduced sensitivity involves more than not detecting carcinogens. Many national and international organizations (e.g., IARC, the NTP in its Annual Report on Carcinogens) generally require

Table 9. Two-species rodent carcinogens detected as one-species carcinogens by a reduced protocol of male rats and female mice

Chemical	Carcinogenicity outcome				Number of target sites	
	MR	FR	MM	FM	Full	Reduced
Benzofuran	–	+	+	+	4	3
Chlorendic acid	+	+	+	–	2	2
p-Chloroaniline HCl	+	E	+	–	4	2
HC blue 1	E	+	+	+	2	1
1,2,3,6,7,8- and 1,2,3,7,8,9-HCDD	E	+	+	+	1	1
ICRF-159	–	+	–	+	2	1
Isophosphamide	–	+	–	+	3	1
1,5-Naphthalenediamine	–	+	+	+	5	3
Nitrofurazone	E	+	–	+	2	1
p-Nitrosodiphenylamine	+	–	+	–	1	1
Phenestrin	–	+	+	+	4	3
Tetrachlorvinphos	–	+	+	+	3	1

MR, male rats; FR, female rats; MM, male mice; FM, female mice; + = carcinogenic; – = not carcinogenic; E = equivocal carcinogenic response; full, male and female rats and mice; reduced, male rats and female mice; HCDD; hexachloro-*p*-dibenzodioxin.

evidence of carcinogenicity in two species before a chemical is considered "possibly," "probably," or "reasonably anticipated to be" a human carcinogen. A reduced protocol would miss some of these two-species carcinogens, declaring them to be one-species carcinogens. For the NCI/NTP database, 12 two-species carcinogens would have been reduced to one-species carcinogens using a reduced protocol of male rats and female mice, and these chemicals are summarized in Table 9.

Unlike the chemicals in Table 8, most of these chemicals produced carcinogenic effects at multiple target sites. The toxicities (MTDs) of these chemicals were similar on average to those of other carcinogens in the NCI/NTP database, and half of these chemicals that were tested in *Salmonella* (4/8) were positive. Even so, only 1 of these12 chemicals (chlorendic acid) is listed in the NTP Sixth Annual Report on Carcinogens as 1 of the 150 substances and medical treatments "reasonably anticipated to be [human] carcinogens" (*14*). Chlorendic acid is also the only 1 of these 12 chemicals considered by IARC to be a "possible" human carcinogen (*15*).

If these two types of sensitivity loss are considered collectively, less than 10% (27/313) of the chemicals evaluated by the NCI/NTP (17% of the carcinogens) would have shown some sensitivity loss by the use of a reduced protocol of male rats and female mice. Moreover, of these 27 chemicals, only one is currently considered by the NTP or IARC to be a likely or possible human carcinogen.

It must be noted that the NTP Annual Report on Carcinogens (*14*) has exposure and production criteria that may not have been met by certain chemicals in Tables 8 and 9. Further, less than half of the chemicals in these two tables has been formally evaluated by IARC in its series of monographs. Nevertheless, our evaluation suggests that the carcinogens missed by using a reduced protocol of male rats and female mice may not be those chemicals most likely to pose a carcinogenic threat to humans.

A further consideration in the decision of whether to use a reduced protocol is the possible loss of supporting information in one sex when interpreting results in the other sex. That is, because of the high correlation in carcinogenic response between males and females, there may be instances in which a borderline carcinogenic effect in one sex–species group would be called positive rather than equivocal or negative because of a similar carcinogenic effect at that same site in the other sex of that species. This supporting information would be lost in a reduced protocol of one sex of each species. However, an evaluation of the magnitude of the carcinogenic responses in recent NCI/NTP studies suggests that this type of sensitivity loss would not be a frequent occurrence.

The loss of sensitivity associated with a reduced protocol must be balanced against the possible advantages of evaluating more chemicals and/or reallocating resources to basic mechanistic studies. Although our evaluation suggests that this more limited experimental design is an option that may be appropriate in some instances, the decision of whether to use such a reduced protocol is best made on a case-by-case basis.

In conclusion, our evaluation 1) shows that the previously reported high male–female and interspecies correlations in carcinogenic response also hold for many site-specific neoplasms, 2) identifies significant associations in site-specific carcinogenic responses that may be useful in further research efforts; and 3) suggests that because of the high correlation in carcinogenic response between males and females, in many cases a reduced protocol of one sex of each species may be sufficient to detect rodent carcinogenicity.

References

1. Haseman JK, Huff JE, Zeiger E, McConnell EE. Comparative results of 327 chemical carcinogenicity studies. Environ Health Perspect 74:229–235(1987).
2. Huff JE, Cirvello J, Haseman J, Bucher J. Chemicals associated with site-specific neoplasia in 1394 long-term carcinogenesis experiments in laboratory rodents. Environ Health Perspect 93:247–270(1991).
3. Huff J, Haseman J, Rall D. Scientific concepts, value and significance of chemical carcinogenesis studies. Annu Rev Pharmacol Toxicol 31:621–652(1991).
4. Haseman JK, Tharrington EC, Huff JE, McConnell EE. Comparison of site-specific and overall tumor incidence analyses for 81 recent National Toxicology Program carcinogenesis studies. Regul Toxicol Pharmacol 6:155–170(1986).
5. Gold LS, Bernstein L, Magaw R, Slone TH. Interspecies extrapolation in carcinogenesis: prediction between rats and mice. Environ Health Perspect 81:211–219(1989).
6. Gold LS, Slone TH, Manley NB, Bernstein L. Target organs in chronic bioassays of 533 chemical carcinogens. Environ Health Perspect 93:233–246(1991).
7. Haseman JK, Zeiger E, Shelby MD, Margolin BH, Tennant RW. Predicting rodent carcinogenicity from four in vitro genetic toxicity assays: an evaluation of 114 chemicals studied by the National Toxicology Program. J Am Stat Assoc 85:964–971(1990).
8. Haseman JK, Huff JE. Species correlation in long-term carcinogenicity studies. Cancer Lett 37:125–132(1987).
9. McConnell, EE. Thyroid follicular cell carcinogenesis: results from 343 two year carcinogenicity studies conducted by the NCI/NTP. Regul Toxicol Pharmacol 16:177–188(1992).
10. Ashby J, Tennant RW. Chemical structure, *Salmonella* mutagenicity, and extent of carcinogenicity as indicators of genotoxic carcinogenesis among 222 chemicals tested in rodents by the U.S. NCI/NTP. Mutat Res 204:17–115(1985).
11. Gold, LS, Slone, TH, Stern, BR, Bernstein, L. Comparison of target organs of carcinogenicity for mutagenic and non-mutagenic chemicals. Mutat Res (in press).
12. Maronpot RR, Haseman JK, Boorman GA, Eustis SL, Rao GN, Huff JE. Liver lesions in B6C3F1 mice: the National Toxicology Program experience and position. Arch Toxicol (suppl 10):10–26(1987).
13. Haseman JK, Seilkop SK. An examination of the association between maximum tolerated dose and carcinogenicity in 326 long-term studies in rats and mice. Fundam Appl Toxicol 19:207–213(1992).
14. NTP. Sixth annual report on carcinogens. Research Triangle Park, NC: National Toxicology Program, 1991.
15. IARC. IARC monographs on the evaluation of carcinogenic risks to humans, vol 48. Some flame retardants and textile chemicals, and exposures in the textile manufacturing industry. Lyon: International Agency for Research on Cancer, 1990.