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Investigation of Independence in Inter-Animal Tumor-Type Occurrences within the NTP Rodent-Bioassay Database

**Report prepared for the
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by

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Abstract

Statistically significant elevation in tumor incidence at multiple histologically distinct sites is occasionally observed among rodent bioassays of chemically induced carcinogenesis. If such data are to be relied on (as they have, e.g., by the U.S. EPA) for quantitative cancer potency assessment, their proper analysis requires a knowledge of the extent to which multiple tumor-type occurrences are independent or uncorrelated within individual bioassay animals. Although difficult to assess in a statistically rigorous fashion, a few significant associations among tumor-type occurrences in rodent bioassays have been reported. However, no comprehensive studies of animal-specific tumor-type occurrences at death or sacrifice have been conducted using the extensive set of available NTP rodent-bioassay data, on which most cancer-potency assessment for environmental chemicals is currently based. This report presents the results of such an analysis conducted on behalf of the National Research Council's Committee on Risk Assessment for Hazardous Air Pollutants. Tumor-type associations among individual animals were examined for ~2500 to 3000 control and ~200 to 600 treated animals using pathology data from 62 B6C3F1 mouse studies and 61 F/344N rat studies obtained from a readily available subset of the NTP carcinogenesis bioassay database. No evidence was found for any large correlation in either the onset probability or the prevalence-at-death or sacrifice of any tumor-type pair investigated in control and treated rats and mice, although a few of the small correlations present were statistically significant. Tumor-type occurrences were in most cases nearly independent, and departures from independence, where they did occur, were small. This finding is qualified in that tumor-type onset correlations were measured only indirectly, given the limited nature of the data analyzed.

Introduction

The EPA (1986) cancer-risk guidelines require the default use of a classical multistage model to extrapolate cancer risk based on observed animal bioassay data when adequate epidemiological data are not available for this purpose. The issue of how to use bioassay data that indicate dose-related effects for multiple tumor types is addressed by these guidelines as follows:

To obtain a total estimate of carcinogenic risk, animals with one or more [histologically distinct] tumor sites or types showing significantly elevated tumor incidence should be pooled and used for [risk] extrapolation. The pooled estimates will generally be used in preference to risk estimates based on single types or sites.

However, if the multistage risk-extrapolation model is assumed and if different histologically related sites or types of tumors observed to be significantly elevated above background rates are known to occur in a statistically independent fashion among the individual bioassay animals tested, the EPA-recommended procedure relying on aggregate tumor incidence as input may lead to biased estimates of aggregate potency or risk. Under the independence assumption, pooled tumor-incidence data may exclude information relevant to dose-response extrapolation, in that multiple tumor types observed within a single animal given a high chronic dose might, at very low doses, not be expected to cluster within single animals (Bogen, 1990). For potency estimates based on classical multistage-type models, this statistical problem is avoided completely if aggregate potency is estimated as the sum of tumor-type-specific potencies (Bogen, 1990). If this approach is used, then aggregate increased risk P of incurring one or more of n significant tumor types given a very low dose D may be estimated by

$$P \approx 1 - \exp\left(-\sum_{i=1}^n q_i D\right) \approx \sum_{i=1}^n q_i D, \quad \text{for } P \ll 1. \quad (1)$$

Of course, the type-specific potencies q_i are uncertain quantities estimated from bioassay data, so appropriate Monte-Carlo procedures generally must be used to perform the summation indicated in (1).

This alternative to EPA's procedure for estimating aggregate cancer potency depends on the validity of the independent-action assumption regarding the occurrence of different tumor types in any given group of bioassay animals (conditional on the marginal incidence rates for those tumor types for the entire group). The independent-action assumption is certainly consistent with the biological premise of classical multistage models that spontaneous as well as dose-induced tumors arise primarily from random or induced DNA damage in target cells within different tissues, provided the different animals tested are all approximately equally susceptible to background and dose-related events giving rise to tumors. If significant inter-animal heterogeneity exists, the occurrence of multiple tumor types would be expected to cluster within the more susceptible individuals.

In some of the few studies that have focused on tumor-type associations within individual animals, a few significant associations have been noted, mostly negative associations involving one or two specific tumor types among associated pairs. Significant ($p < 0.05$) age- and treatment-adjusted associations for five of 21 sex-specific pairs from six tumor types investigated were reported by Breslow et al. (1974) for experiments involving over 4000 CF-1 mice exposed to DDT, urethane or nothing: negative associations between lymphomas and each of hepatomas (males), lung adenomas (males and females), and mammary and ovarian tumors (females), and a positive association between lymphomas and bone tumors (males). (Upon adjustment for multiple significance tests (Wright, 1992), the association between lymphomas and mammary tumors observed in that study may not be significant at the 0.05 level.) Breslow et al. (1974) suggested that the negative lymphoma-related associations, except perhaps those involving liver tumors, were all likely to be spurious, "due to the relative

rapidity with which lymphomas tend to kill their bearers." A significant negative association between lymphomas and liver tumors (but not lung tumors) in 1478 similarly exposed CF-1 mice was later confirmed, even after accounting for the relatively rapid lymphoma lethality by use of serial sacrifice information (Wahrendorf 1983). A significant negative correlation between malignant lymphoma and proliferative hepatocellular lesions at death/sacrifice was also found among 1858 male ICI mice (Young and Gries, 1984). Haseman (1983) also noted this significant negative correlation in raw tumor-incidence data for F344 rats from 25 National Toxicology Program (NTP) bioassays (not analyzed at the level of individual animals).

The most comprehensive study of this type involved an examination of age- and treatment-adjusted associations between (66 possible) pairs of 12 tumor types at death/sacrifice in 3813 gamma-irradiated female BALB/c mice reported 21 significant ($p < 0.05$) positive or negative associations, 10 of which were negative and involved reticular tumors considered to be rapidly lethal and generally also involved other tumors considered to be lethal in the animals studied; most of these 10 associations were considered to be spurious due to the effect of lethality (Storer, 1982). The remaining associations considered significant generally were positive and involved endocrine-related tumors (Harderian, mammary, adrenal, and pituitary tumors), and none of these involved liver tumors. Aside from associations involving reticular sarcomas, and after appropriate statistical adjustment for multiple tests of significance (Wright, 1992), only three of 55 remaining possible associations reported by Storer (1982) appear to be significant at a 0.05 level, all involving Harderian-gland tumors, which, along with ovary, adrenal and pituitary tumors, were all considered to be nonlethal in the animals studied. A recent study of liver-tumor and reticulum-cell-sarcoma incidence in 1004 gamma-irradiated female C3H mice supported a significant negative correlation of these tumor types, even after adjustment for the relative lethality of the reticular tumors using cause-of-death information available in that study (Mitchell and Turnbull, 1990).

In other smaller studies, an assumption of independence in tumor-types at death/sacrifice was shown to be consistent with ED₀₁ data on four different tumor types in 366 control female BALB/c mice and six tumor types elevated in 193 such mice exposed to 2-acetylaminofluorine (Finkelstein and Schoenfeld, 1989), as well as with Hazelton Laboratory data on three different tumor types elevated in a total of 142 male albino rats exposed to dibromochloropropane (Bogen, 1990).

No comprehensive study of animal-specific tumor-type occurrences at death/sacrifice has been conducted using the extensive set of available NTP rodent-bioassay data, on which most cancer-potency assessment for environmental chemicals is currently based. This report presents the results of such an analysis conducted on behalf of the National Research Council's Committee on Risk Assessment for Hazardous Air Pollutants.

Data Description

Tumor-type associations among individual animals were examined for both control and treated animals using pathology data from 62 B6C3F1 mouse studies and 61 F/344N rat studies obtained from a readily available subset of the NTP carcinogenesis bioassay database. Most studies were 2-year studies, although a few were shorter (e.g., 15 months). Separate analyses were conducted for the four sex/species combinations (male and female mice, male and female rats) corresponding to the compounds and species indicated in Table 1. Analysis was confined to the following common tumor types (occurring at a rate >5%):

Rats:	Adrenal gland:	medulla pheochromocytomas (benign or malignant)
	Thyroid gland:	C-cell adenomas or carcinomas
	Pituitary gland:	carcinomas or adenomas
	Mammary gland:	fibromas, fibroadenomas, carcinomas, or adenomas
	Leukemia:	lymphocytic, monocytic, mononuclear, or undifferentiated.

Mice:	Lung:	alveolar/bronchiolar adenomas or carcinomas
	Liver:	hepatocellular adenomas, hepatocellular carcinomas, and hepatoblastomas
	Lymphoma:	histiocytic, lymphocytic, mixed, NOS, or undifferentiated.

Analyses of correlations between tumor occurrence in treated animals were based on subsets of the control-animal data, comprising studies for which the NTP declared "clear evidence" of an effect at multiple sites and for which pairs of such effects were exhibited in more than one study (resulting in the use of five rat studies and four mouse studies). The treated animal studies involved tumor types that differed from the control-animal studies, namely, adenomas or carcinomas of: liver, Zymbal's gland, clitoral /preputial gland, and skin in rats; and liver, adrenal and Harderian gland in mice. In both control- and treated-animal analyses, evidence of associations from individual studies were pooled as described below.

Statistical Methods

Associations among statistically significantly elevated tumor-types within individual animals may pertain either to tumor onset probabilities or to prevalence at death/sacrifice or to both. It is well known that associations present at death/sacrifice may differ, sometimes substantially, from those relating to tumor onset, and that the former may be heavily influenced by the latter as a result of the time-dependent action of competing risks (Hoel and Walburg, 1972; Breslow et al., 1974; Wahrendorf, 1983; Lagakos and Ryan, 1985). For example, if the onset probabilities of two different tumor types are statistically independent, but in addition both are rapidly lethal, then there is little probability of their joint occurrence within an individual animal and thus their prevalence at death/sacrifice will be negatively correlated. This fact was the basis for concluding probable "spurious" negative correlations involving rapidly lethal tumor types in previous assessments of tumor-type associations in rodents (Breslow et al., 1974; Storer, 1972).

Unambiguous detection of associations in onsets of different tumor types requires either serial-sacrifice information or animal- and tumor-specific lethality information (Hoel and Walburg, 1972; Wahrendorf, 1983; Lagakos and Ryan, 1985; Mitchell and Turnbull, 1990), neither of which is available for the NTP data analyzed here. Thus, the present analysis was primarily restricted to an assessment of age-adjusted correlations in tumor-types present at death/sacrifice. This approach provides definitive information on onset (as well as terminal prevalence) correlations only if all tumor types are incidental to fatality. However, as described below, a crude assessment of onset-probability correlations was also conducted using information on tumor lethality obtained from the data studied.

Evaluation of the correlations between occurrences between pairs of tumor types in individual animals observed at death/sacrifice was based on age-adjustment of information from 2×2 contingency tables that were constructed for pairs of tumor occurrences, as in previous similar studies (Breslow et al, 1974; Storer, 1982; Young and Gries, 1984; Finkelstein and Schoenfeld, 1989). Five survival-age strata within each study were used: (1) first 365 days, (2) 366-546 days (1.5 years), (3) 547-644 days (~1.75 years), (4) 644-terminal sacrifice (~2 years), (5) terminal sacrifice. Further stratification addressed the inclusion of the highest two dose groups. Thus, the potential number of analytical strata (i.e., 2×2 tables) was the number of studies times 5 (the number of temporal strata) times 2 (the number of dose levels). The method of Mantel and Haenszel (1959) was used to combine results from stratum-specific contingency tables and to assess two-tailed significance of overall associations between tumor occurrences. Overall correlations are represented as the weighted averages of corresponding stratum-specific measures, using the numbers of animals in the strata as weights. Adjusted p-values accounting for multiple tests of a zero-correlation null hypothesis were obtained for all control and all treated rats and mice using Hommel's modified Bonferroni procedure (Wright, 1992).

In the absence of serial sacrifice or lethality information, associations between onsets of pairs of tumor types in individual NTP-bioassay animals were evaluated using two crude techniques. First, a separate correlation analysis was undertaken as above, but using only terminal sacrifice data. This approach provides definitive information on onset (as well as terminal prevalence) correlations only if no animals die prior to terminal sacrifice, but may nevertheless provide meaningful information if a sufficiently large fraction of animals survive until sacrifice. The second approach used was the three-by-three contingency-table method for detection of disease-onset associations devised by Mitchell and Turnbull (1990), which requires lethality determinations for each tumor occurrence in each animal. When in doubt regarding such lethality, Mitchell and Turnbull (1990) recommend that it would be prudent to classify a particular occurrence as lethal, because while doing so falsely may reduce the power of the test, the null distribution will not be affected. Thus, the Mitchell-Turnbull test was applied under the assumption that all occurrences of a given tumor type were lethal for all plausibly lethal tumor types. Tumor-type lethality was investigated using Mann-Whitney U statistics comparing survival times of tumor-bearing and tumor-free animals, where all study-specific results for a given control or treated species and sex were combined to form an overall test by summing these U statistics and dividing this sum by the square root of the sum of the corresponding variances.

Results and Discussion

The results of our analysis of correlations in incidence at death/sacrifice of tumor types in control rats and mice are summarized in Table 2. These results indicate four significant ($p^* \leq 0.05$) but small correlations among 20 sex/tumor-type-pairs investigated in rats (pituitary vs. leukemia in both sexes, and mammary vs. leukemia or pituitary in females—where all those involving leukemia were negative), and no similarly significant correlations among 12 sex/tumor-type-pairs investigated in mice. Corresponding results

for treated rats and mice are summarized in Table 3. Significant ($p^* \leq 0.05$) but again generally quite small correlations appear present for two of 12 sex/tumor-type-pairs investigated in treated rats (Zymbal's vs. preputial gland and liver vs. skin tumors in males) and for one of four sex/tumor-type-pairs investigated in treated mice (liver vs. Harderian gland in females), where the liver-related correlations were both positive.

Terminal-sacrifice animals represented 66 to 68% of all the control mice and 53 to 63% of all control rats referred to in Table 2. Analysis of tumor-type-prevalence correlations in those animals revealed only a single significant ($p^* \leq 0.05$) correlation, that between mammary and pituitary tumors in female rats ($r=0.080$, $p^*=0.013$). Thus, the latter positive (albeit quite small) correlation may pertain to onset as well as prevalence-at-death/sacrifice correlations, whereas the negative leukemia-related correlations noted above for all control rats did not persist in terminal-sacrifice animals. This finding could be explained by relative lethality associated with rodent leukemia/lymphoma, which has been noted in previous studies (Breslow et al., 1974; Wahrendorf, 1983; Young and Gries, 1984; Portier et al., 1986). Terminal-sacrifice animals represented only 14 to 16% of all the treated rats and 20 to 55% of all treated mice referred to in Table 3. Correlation analyses for these treated animals yielded no significant ($p^* \leq 0.05$) correlations, which result sheds less light on tumor-onset associations given the greater non-representativeness of these animals.

Our examination of differences in survival time in animals with particular tumors vs. tumor-free animals revealed a few significant differences in control and treated rats. Leukemia in both sexes of control F344 rats studied was associated with a significant reduction in mean survival time ($p<0.001$). However, this reduction was rather modest: 75% of leukemia-bearing animals lived until the 23rd month of the studies and 50% lived until terminal sacrifice. In contrast, 75% of the leukemia-free animals survived until terminal sacrifice. Thus, any effect of leukemia lethality in inducing negative correlations with other cancers is likely to be small.

There was also evidence that Zymbal's gland tumors in treated rats resulted in reduced survival times (males, $p < 0.001$; females, $p = 0.003$), where the median survival times were reduced by about four months in males (546 vs. 427 days—a reduction more striking than that for leukemia in control males) and by about one month in females. When leukemia and Zymbal's gland tumors in animals dying before terminal sacrifice were assumed to be lethal and all other tumor types incidental, the Mitchell-Turnbull test yielded similar results to those obtained using the unmodified age-stratified analysis. In particular, it provided strong evidence that the small, negative associations between leukemia and pituitary-gland tumors in control rats were not due to chance or to differential lethality (males, $p < 10^{-9}$; females, $p = 0.000057$), and it indicated the same regarding the small, negative associations between Zymbal's-gland tumors and preputial-/clitoral-gland tumors in treated rats ((males, $p = 0.009$; females, $p = 0.002$).

In summary, no evidence was found for any large correlation in either the onset probability or the prevalence-at-death/sacrifice of any tumor-type pair investigated in control and treated rats and mice, although a few of the small correlations present were statistically significant. This finding must be qualified to the extent that tumor-type onset correlations were measured indirectly given the limited nature of the data analyzed. Taken together, these findings indicate that tumor-type occurrences in B6C3F1 mice and F344 rats used in the NTP bioassays analyzed were in most cases nearly independent, and that departures from independence, where they did occur, were small.

Some of the significantly correlated sites in our analysis of treated animals correspond to site-pairs for which associations between experimental outcomes were recently determined to be statistically significant by Haseman and Lockhart (1992). Our analysis, however, fundamentally differs from theirs in that we examined tumor-type-occurrence correlations among individual animals in each study considered, while they examined correlations between tumor-type-specific positivity across different studies. For example, Haseman and Lockhart reported a significant relationship ($p < 0.001$)

between experimental outcomes of chemicals on the liver and Zymbal's gland in rats. Thus, an experiment in which a significant liver effect occurred was more likely to have an significant effect in Zymbal's gland than those experiments in which there were no effects on the liver. The results of our analysis at the level of individual animals indicates no evidence of this association at this level (Table 3). Thus, the two analyses suggest that the relationship between liver and Zymbal's gland effects reflects similarity between chemicals rather than a predisposition for individual animals to display both of these effects. Unfortunately, our analysis was based on only a subset of the studies that Haseman and Lockhart utilized. Future work will extend the results of our study to include all the experiments utilized by Haseman and Lockhart.

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Table 1

NTP STUDIES FROM WHICH DATA WERE USED

CHEMICAL	MICE ^a	RATS ^a
0-CHLOROBENZALMALONONITRILE (CS-2)		X
1,2,3-TRICHLOROPROPANE	X ^b	X ^c
1,3-BUTADIENE (BUTADIENE)	X	
2,4-DIAMINOPHENOL DIHYDROCHLORIDE	X	X
2,4-DICHLOROPHENOL	X	X
3,3'-DIMETHOXIBENZIDINE DIHYDROCHLORIDE		X ^{c,d}
3,3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE		X ^{c,d}
4,4-DIAMINO-2, 2-STILBENEDISULFONIC ACID	X	X
4-HYDROXYACETANILIDE	X	X
4-VINYL-1-CYCLOHEXENE DIEPOXIDE	X	X
ALLYL GLYCIDYL ETHER	X	
ALPHA-CHLOROACETOPHENONE	X	X
BENZALDEHYDE	X	X
BENZYL ACETATE	X	X
BROMOFORM	X	X
C.I. ACID RED 114		X ^{c,d}
C.I. DIRECT BLUE 15		X ^{c,d}
CARVONE	X	
CHLORAMINE	X	X
CI PIGMENT RED 23	X	X
CI PIGMENT RED 3	X	X
COUMARIN	X	X
DICHLORVOS	X	X
DIHYDROCOUMARIN	X	X
DIMETHOXANE	X	X
DIPHENYLHYDANTOIN	X	X
DL AMPHETAMINE SULFATE	X	X
DOWICIDE EC-7 PENTACHLOROPHENOL	X	
EPINEPHRINE HCL	X	X
ETHYL CHLORIDE	X	X
ETHYLENE GLYCOL	X	
ETHYLENETHIOUREA	X	X
FIREMASTER FF-1 POLYBROMINATED BIPHENYL	X	X
FURAN	X ^e	X
FURFURAL	X	X
GAMMA-BUTYROLACTONE	X	X
HC YELLOW 4	X	X
HEXACHLOROETHANE		X
HYDROQUINONE	X	X

NTP STUDIES FROM WHICH DATA WERE USED (Table 1, continued)

CHEMICAL	MICE	RATS
MANGANESE SULFATE	X	X
MERCURIC CHLORIDE	X	X
METHYL BROMIDE	X	
MONOCHLOROACETIC ACID	X	X
N-METHYLOLACRYLAMIDE	X ^b	X
NAPHTHALENE	X	
NITROFURANTOIN	X	X
O-CHLOROBENZALMALONONITRILE (CS-2)	X	
O-NITROANISOLE	X	X
OCHRATOXIN A		X
P-NITROANILINE	X	
PARA-CHLOROANILINE	X	X
PENTACHLOROANISOLE	X	X
PENTAERYTHRITOL TETRANITRATE	X	X
PENTACHLOROPHENOL, DOWICIDE EC-7	X ^e	
PENTACHLOROPHENOL, TECHNICAL GRADE	X	
PHENYLBUTAZONE	X	X
POLYSORBATE 80	X	X
PROBENECID	X	X
QUERCETIN		X
RESORCINOL	X	X
RHODAMINE 6G	X	X
ROXARSONE	X	X
SODIUM AZIDE		X
SODIUM FLUORIDE	X	X
SUCCINIC ANHYDRIDE		X
TALC	X	
TETRANITROMETHANE	X	X
TITANOCENE DICHLORIDE		X
TOLUENE	X	X
TRIAMTERENE	X	X
TRIS (2-CHLOROETHYL) PHOSPHATE	X	X
VINYL TOLUENE	X	X

^aNTP studies from which treated-animal data, in addition to control animal data, were taken for use in this analysis are indicated by a superscript.

^bLiver and Harderian-gland effects in treated animals.

^cZymbal's-gland and clitoral-/preputial-gland effects in treated animals.

^dLiver and skin effects in treated animals.

^eLiver and adrenal-gland effects in treated animals.

Table 2**CORRELATIONS BETWEEN TUMOR PREVALENCE AT DEATH/SACRIFICE
IN CONTROL GROUPS**

SPECIES					
Tumor Types	Sex	Corr.	n	p-value	Adjusted p-value
RATS					
Adrenal × Leukemia	Females	0.060	2794	0.017	0.272
	Males	0.025	2786	0.257	0.982
Adrenal × Thyroid	Females	0.041	2692	0.138	0.967
	Males	-0.024	2593	0.342	0.982
Thyroid × Leukemia	Females	-0.032	2942	0.120	0.960
	Males	-0.045	2827	0.076	0.783
Pituitary × Leukemia	Females	-0.158	3057	1.0 10 ⁻⁹	2.0 10 ⁻⁸
	Males	-0.080	2990	0.000074	0.0013
Mammary × Leukemia	Females	-0.074	3088	0.00018	0.00306
	Males	-0.025	3045	0.356	0.982
Mammary × Pituitary	Females	0.076	3057	0.00011	0.0019
	Males	0.027	2990	0.301	0.982
Pituitary × Thyroid	Females	-0.002	2916	0.982	0.982
	Males	0.026	2784	0.254	0.982
Pituitary × Adrenal	Females	-0.029	2770	0.268	0.982
	Males	-0.010	2739	0.659	0.982
Mammary × Adrenal	Females	-0.015	2794	0.597	0.982
	Males	0.008	2786	0.835	0.982
Mammary × Thyroid	Females	-0.011	2942	0.642	0.982
	Males	0.008	2827	0.846	0.982
MICE					
Liver × Lung	Females	-0.003	3058	0.978	0.978
	Males	-0.022	3011	0.322	0.978
Liver × Lymphoma	Females	-0.029	3059	0.185	0.978
	Males	-0.053	3014	0.017	0.187
Lung × Lymphoma	Females	-0.054	3071	0.018	0.198
	Males	-0.008	3016	0.791	0.978
Pituitary × Lung	Females	0.014	2898	0.592	0.978
	Males	0.025	2725	0.879	0.978
Pituitary × Liver	Females	0.020	2891	0.393	0.978
	Males	-0.074	2724	0.307	0.978
Pituitary × Lymphoma	Females	-0.041	2899	0.058	0.580
	Males	0.011	2727	0.806	0.978

Table 3

**CORRELATIONS BETWEEN TUMOR PREVALENCE AT DEATH/SACRIFICE
IN CHEMICALLY AFFECTED TREATMENT GROUPS**

SPECIES					
Tumor Types	Sex	Corr.	n	p-value	Adjusted p-value
RATS					
Liver × Zymbal's Gland	Females	0.005	498	0.927	0.961
	Males	0.004	499	0.961	0.961
Zymbal's Gland × Clitoral/Preputial Gland	Females	-0.117	590	0.012	0.12
	Males	-0.152	577	0.003	0.033
Skin × Zymbal's Gland	Females	-0.065	500	0.272	0.961
	Males	-0.071	500	0.213	0.961
Liver × Skin	Females	0.041	498	0.630	0.961
	Males	0.172	498	0.002	0.022
Liver × Clitoral/Preputial Gland	Females	0.034	488	0.658	0.961
	Males	-0.078	487	0.187	0.961
Skin × Clitoral/Preputial Gland	Females	0.023	489	0.762	0.961
	Males	0.027	487	0.735	0.961
MICE					
Liver × Adrenal Gland	Females	0.153	194	0.245	0.49
	Males	0.257	196	0.076	0.228
Liver × Harderian Gland	Females	0.236	190	0.004	0.016
	Males	0.024	191	0.889	0.889

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