

Fw: Re: revised TCE PBPK comments for SAB  
Paul Dugard  
to:  
Marc Rigas  
05/03/2010 09:36 PM  
Please respond to Paul Dugard  
Show Details

Dear Dr Rigas:

Dr Dourson's presentation on May 10 will be based on the comments that were filed by the Aerospace Industries Alliance during the public review period for the IRIS draft. The text of those comments have been abstracted and attached for the convenience of the TCE panel the tables referred to by Dr Dourson in his message to the panel that follows are also attached.

With best wishes.

Paul Dugard

-----Forwarded Message-----

From: Michael Dourson  
Sent: May 3, 2010 5:10 PM  
To: Paul Dugard  
Cc: Lynne Haber , Lisa Sweeney  
Subject: Re: revised TCE PBPK comments for SAB

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Dear Colleagues

We appreciate the opportunity to help with this complex assessment. We note that a portion of our previous submittal was not incorporated into the otherwise nice summary table of all reviewer comments. Specifically, Tables 1 through 10 of comment "TCE Chapter 4.11.2; excerpt ID 201" are mentioned, but apparently were not provided to the SAB. Because these tables summarize data analyzed from EPA's text that would aid the SAB in the understanding of our comments, they are now attached in PDF format. These tables list our judgments of the biological significance of all the relevant tumors found in the experimental animal studies.

We agree with EPA that several of these experimental animal studies have problems. In part because of this, we agree with EPA that it is important to look at this experimental animal database holistically. As can be seen from the attached tables, however, EPA's description of this evidence is unconvincing when starting from the neutral question of: "Does TCE cause cancer in experimental animals?" Of the 4 primary tissues that EPA evaluates for carcinogenicity, only one or perhaps two of them, liver and lung tumors in mice, rises to the level of biological significance. Discussion of the remaining tumor types appears to presuppose that TCE is carcinogenic.[1] The resulting text appears then to overly discount negative data, of which there are many, and to highlight marginal findings. The text does not appear to be a dispassionate rendering of the totality of the available data.

Because of this, the carcinogenicity weight of evidence appears to be forced, inadvertently, to a finding of "carcinogenic to humans." Depending on how the epidemiology evidence is

judged, this weight of evidence should be no more than “likely to be carcinogenic to humans.” Based on the experimental animal evidence alone, this weight of evidence can be no more than “suggestive evidence of carcinogenicity.”

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[1] While assessments under the 2005 EPA guidelines are based on a weight-of-evidence evaluation of all available data, rather than separate analyses of the animal and human data, the human data alone are not sufficient to create the presupposition of carcinogenicity, as discussed in our original comments and those of Exponent Health Services.

Sincerely,

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**Comments on the Weight of Evidence Cancer Conclusions in the Trichloroethylene:  
Consideration of Both Toxicological and Epidemiologic Evidence - External Review Draft**

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**Summary**

These comments address the question of whether the overall toxicological and epidemiologic data provide sufficient evidence for description of TCE as “Carcinogenic to Humans.” First we review the Environmental Protection Agency’s (EPA’s) 2005 guidelines for weight of evidence descriptors regarding carcinogenic potential . We then consider where the scientific evidence from toxicological and epidemiologic research best fits under these criteria.

Our key overall observations and conclusions are as follows: EPA has proposed a cancer descriptor of “carcinogenic to humans” for TCE “based on convincing evidence of a causal association between TCE exposure in humans and kidney cancer.”

Upon a critical scientific assessment, we find that the currently available are clearly not convincing of a causal association between TCE exposure and cancer in humans. This is because neither the epidemiologic data nor the animal and mechanistic data meet EPA’s criteria of "carcinogenic to humans" as described in the 2005 EPA Guidelines for Carcinogen Risk Assessment. Moreover, we find that EPA has not judged any other chemical as a "human carcinogen" or its equivalent (using older guidelines) on such inconsistent support and such a lack of strong and convincing epidemiologic evidence. EPA's proposal to use the classification

"carcinogenic to humans" for TCE would be a poorly supported precedent in the application of its own guidelines.

Rather, our judgment based on the 2005 EPA Guidelines for Carcinogen Risk Assessment, which EPA has established to make such determinations consistent across chemical assessments, indicates that a more correct classification for EPA to make for TCE would either be "likely to be carcinogenic to humans" or "suggestive evidence of carcinogenicity" depending on how one considers the "adequacy" of evidence to demonstrate carcinogenic potential.

### **Summary of EPA Guidelines**

The EPA's (2005) Guidelines for Carcinogen Risk Assessment suggest the following descriptors as an introduction to the weight of evidence (WOE) narrative, noting that the entire narrative provides the conclusions and the basis for them:

- Carcinogenic to humans,
- Likely to be carcinogenic to humans,
- Suggestive evidence of carcinogenicity,
- Inadequate information to assess carcinogenic potential, and
- Not likely to be carcinogenic to humans.

According to the guidelines, the descriptor "**carcinogenic to humans**" "indicates strong evidence of human carcinogenicity. It covers different combinations of evidence.

- "This descriptor is appropriate when there is convincing epidemiologic evidence of a causal association between human exposure and cancer.

- Exceptionally, this descriptor may be equally appropriate with a lesser weight of epidemiologic evidence that is strengthened by other lines of evidence. It can be used when *all* [italics added] of the following conditions are met: (a) there is strong evidence of an association between human exposure and either cancer or the key precursor events of the agent's mode of action (MOA) but not enough for a causal association, and (b) there is extensive evidence of carcinogenicity in animals, (c) the mode(s) of carcinogenic action and associated key precursor events have been identified in animals, and (d) there is strong evidence that the key precursor events that precede the cancer response in animals are anticipated to occur in humans and progress to tumors, based on available biological information. In this case, the narrative includes a summary of both the experimental and epidemiologic information on MOA and also an indication of the relative weight that each source of information carries, e.g., based on human information, based on limited human and extensive animal experiments.”

According to the guidelines, the descriptor “**likely to be carcinogenic to humans**” is “appropriate when the weight of the evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor ‘Carcinogenic to Humans.’ Adequate evidence consistent with this descriptor covers a broad spectrum....

Supporting data for this descriptor may include:

- an agent demonstrating a plausible (but not definitively causal) association between human exposure and cancer;
- an agent that has tested positive in animal experiments in more than one species, sex, strain, site or exposure route, with or without evidence of carcinogenicity in humans;

- a positive tumor study that raises additional biological concerns beyond that of a statistically significant result, for example, a high degree of malignancy or an early age at onset;
- a rare animal tumor response in a single experiment that is assumed to be relevant to humans; or
- a positive tumor study that is strengthened by other lines of evidence.”

According to the guidelines, the descriptor “**suggestive evidence of carcinogenicity**” is “appropriate when the weight of evidence is suggestive of carcinogenicity; a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion. This descriptor covers a spectrum of evidence associated with varying levels of concern for carcinogenicity, ranging from a positive cancer result in the only study on an agent to a single positive cancer result in an extensive database that includes negative studies in other species. Depending on the extent of the database, additional studies may or may not provide further insights. Some examples [of supporting data for this descriptor] include:

- a small, and possibly not statistically significant, increase in tumor incidence observed in a single animal or human study that does not reach the weight of evidence for the descriptor “Likely to Be Carcinogenic to Humans;”
- a small increase in a tumor with a high background rate in that sex and strain, when there is some but insufficient evidence that the observed tumors may be due to intrinsic factors that cause background tumors and not due to the agent being assessed;

- evidence of a positive response in a study whose power, design, or conduct limits the ability to draw a confident conclusion (but does not make the study fatally flawed), but where the carcinogenic potential is strengthened by other lines of evidence; or
- a statistically significant increase at one dose only, but no significant response at the other doses and no overall trend.”

According to the guidelines, the descriptor “**inadequate information to assess carcinogenic potential**” is “appropriate when available data are judged inadequate for applying one of the other descriptors. Additional studies generally would be expected to provide further insights. Some examples include:

- little or no pertinent information;
- conflicting evidence, that is, some studies provide evidence of carcinogenicity but other studies of equal quality in the same sex and strain are negative;
- negative results that are not sufficiently robust for the descriptor, “not likely to be carcinogenic to humans.”

### **Application of the Guidelines to Trichloroethylene**

In considering the data in the context of applying the “carcinogenic to humans” descriptor, one first considers the weight of the epidemiological evidence. We judge the epidemiologic evidence to be neither “convincing” nor “strong,” two key terms in the guidelines. This judgment is based on four recent reviews and meta-analyses of occupational TCE exposures and cancer as well as other reviews of this literature (Alexander et al., 2006, 2007; Mandel et al., 2006; Kelsh et al., 2010). The recent review and meta-analysis by Kelsh et al., 2010 focuses on occupational TCE exposure and kidney cancer, and includes the recent Charbotel 2006 study that is emphasized in the EPA assessment and used by EPA scientists to conduct a quantitative risk

assessment. Both the EPA meta-analysis and the recently published Kelsh et al. meta-analysis of the TCE-kidney cancer epidemiologic literature produced similar summary results. However in Kelsh et al., the limitations of this body of research, namely exposure assessment limitations, potential unmeasured confounding, potential selection biases, and inconsistent findings across groups of studies, did not allow for a conclusion that there is sufficient evidence of a casual association, despite a modest overall association. In addition, although the recent Charbotel et al. 2006 study has made important improvements in exposure assessment, it still has important potential limitations that do not permit an appropriate use in quantitative risk assessment.

There are reasonably well designed and well conducted epidemiologic studies that report no association between TCE and cancer, some reasonably well designed and conducted studies that did report associations between TCE and cancer, and finally some relatively poorly designed studies reporting both positive and negative findings. Overall, the summary relative risks or odds ratios in the meta-analysis studies (EPA or published meta-analyses) generally ranged between 1.2 and 1.4. The IRIS document refers to these associations as “small,” a term not typically consistent with “convincing” and strong.” Weak or small associations may be more likely to be influenced or be the result of confounding or bias. Smoking and body mass index are well-established risk factors for kidney cancer, and smoking and alcohol are risk factors for liver cancer, yet the potential impact of these factors on the meta-analysis associations was not fully considered. There were suggestions that these factors may have impacted findings (e.g. in the large Danish cohort study of TCE exposed workers, the researchers noted that smoking was more prevalent among the TCE exposed populations however little empirical data were provided (Raachou-Nielson et al., 2003). In addition, colinearity of occupational exposures (i.e., TCE exposure correlated with chemical and/or other exposures) may make it difficult to isolate

potential effects of TCE from those of other exposures within a given study, and hinder interpretation across studies. For example, although Charbotel et al. (2006) reported potential exposure response trends, while controlling for many confounders of concern (which strengthens the weight of evidence), they also reported attenuated associations for cumulative TCE exposure after adjustment for exposure to cutting fluids and other petroleum oils (weakening the weight of the evidence). This study is also limited due to other by potential study design considerations such as selection bias, self report of work histories, residual confounding and other design factors.

When examining the data for TCE and non-Hodgkin lymphoma, kidney cancer, and liver cancer, associations were inconsistent across occupational groups (summary results differed between aerospace/aircraft worker cohorts compared with workers from other industries), study design, location of the study, quality of exposure assessment (e.g., evaluating studies that relied upon biomonitoring to estimate exposure vs. semi-quantitative estimates vs. self-report, etc.), and by incidence vs. mortality endpoints. Although EPA examined high dose categories, it did not evaluate any potential dose-response relationships across the epidemiologic studies (except for the Charbotel et al. 2006 study). In our reviews of the epidemiologic data reported in various studies for different exposure levels (e.g. cumulative exposure and duration of exposure metrics), we did not find consistent dose-response associations between TCE and the three cancer sites under review (Mandel et al., 2006; Alexander et al., 2007; Kelsh et al., 2010). An established dose-response trend is one of the more important factors when making assessments of causation in epidemiologic literature. These issues are addressed in greater detail in the accompanying comments by Michael Kelsh and Dominic Alexander.

Thus, based on an overall WOE analysis of the epidemiologic research, these data do not support the conclusion that there is “strong” or “convincing” evidence of a causal association between human exposure and cancer.

The EPA’s 2005 guidelines also state that a chemical may be described as carcinogenic to humans with a lesser weight of epidemiologic evidence that is strengthened by other lines of evidence, all of which must be met. One of these lines of evidence is “extensive evidence of carcinogenicity in animals.” Therefore, we now turn to an evaluation of the animal data.

In weighing the evidence in experimental animals and addressing the impact of the metabolites produced, EPA states that

“A greater variability of response is expected than from exposure to a single agent making it particularly important to look at the TCE database in a holistic fashion rather than the results of a single study, especially for quantitative inferences.” (EPA, page 4-233)

We agree with EPA that the database needs to be viewed holistically. EPA goes on to surmise that evidence for cancer is found in two species (rats and mice) and for more than one tumor endpoint (kidney, liver, lung and immune system). However, EPA’s description of this evidence is unconvincing when starting from the neutral question of: “Does TCE cause cancer in experimental animals?” Of the 4 primary tissues that EPA evaluates for carcinogenicity, only one or perhaps two of them, liver and lung tumors in mice, rises to the level of biological significance. Discussion of the remaining tumor types appears to presuppose that TCE is carcinogenic. The resulting text appears then to overly discount negative data, of which there are many, and to highlight marginal findings. The text does not appear to be a dispassionate rendering of the available data.<sup>1</sup>

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<sup>1</sup> For example, EPA (page 4-261) states “For rats, Maltoni et al. (1986) reported 4 liver angiosarcomas (1 in a control male rat, 1 both in a TCE-exposed male and female at 600 ppm TCE for 8 weeks, and 1 in a

Specifically, EPA's conclusion that kidney cancer is evident in rats rests on one statistically significant finding in over 70 dose/tumor endpoint comparisons and references to exceedances of historical control values (NTP, 1990). Using a 0.05 p-value for statistical significance, a frequency of 1 or even several statistically or biologically significant events is expected in such a large number of dosed/tumor groups. This expectation is met, but not exceeded, as shown in Tables 1 and 2, which present the percent response for the various studies of kidney tumors, grouped by exposure level. EPA notes several other occurrences of kidney tumors, but the incidence was either not statistically significant or of borderline significance in comparison with concurrent controls. The presentation of data vs. the historical NTP controls is very useful. But historical control data needs to be presented in the context of both the study and year, since drift occurs in animal colonies (e.g., it is likely that the historical control data were different for the NCI 1976 study than for the NTP 1988-1990 studies). At least as importantly, historical control data is needed for each strain, particularly in light of the relatively high control response (7% in the inhalation study in Han:Wistar rats (Henschler et al., 1980). The statements about consistent increases of a rare tumor seem to assume that the background for all strains is the same as that reported by NTP for F344 rats. Moreover, each of the studies EPA cites has

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female rat exposed to 600-ppm TCE for 104 weeks), but the specific results for incidences of hepatocellular "hepatomas" in treated and control rats were not given. Although Maltoni et al. (1986) concluded that the small number was not treatment related, the findings were brought forward [emphasis added] because of the extreme rarity of this tumor in control Sprague-Dawley rats, untreated or treated with vehicle materials." Perhaps we missed them in EPA's tome, but these data were not shown.

Another example of this tendency to discount negative findings is found on Page 4-263. "Although the mice in the two experiments [Maltoni et al., 1988, Table 4-55, page 4-258] in males were of the same strain, the background level of liver cancer was significantly different between mice from the different sources (1/90 versus 19/90), though the early mortality may have led to some censoring." Perhaps we missed EPA's point, but it appears that the Table 4-55 only presented one of the two control groups. Inclusion of the control group with the higher background level would suggest that there was no chemical-related increase.

problems. Although EPA generally does a good job of identifying these problems, its overall conclusion, based on these flawed studies cannot be that TCE is a known kidney tumorigen. The best that can be said is that the data are inconsistent.

EPA states that liver tumors are statistically significant in mice. This statement is confirmed by a biological judgment of all available data as shown in Tables 5 and 6.<sup>2</sup>

EPA finds three statistically significant occurrences of lung tumors in mice, 1 of them in a study with known epichlorohydrin contamination. Findings in other studies might be considered as biologically significant (see highlights in Tables 9 and 10 of these comments). The rest of the studies show no statistically significant increase, or show no lung tumors, or show a decrease in lung tumors as shown in Tables 7, 8, 9 and 10. Briefly, these data are either equivocal or marginally positive. EPA might consider revising its lung tumor table (Table 4-73) in order to make this information more readily transparent.

EPA states on page 4-397 that:

“Cancers of the immune system that have been observed in animal studies and are associated with TCE exposure are summarized in Tables 4-68 and 4-69. The specific tumor types observed are malignant lymphomas, lymphosarcomas, and reticulum cell sarcomas in mice and leukemias in rats...

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<sup>2</sup> EPA (page 4-261) also states that “The NTP (1990) study of TCE exposure in male and female F344/N rats, and B6C3F1 mice (500 and 1,000 mg/kg for rats) is limited in the ability to demonstrate a dose-response for hepatocarcinogenicity. For rats, the NTP (1990) study reported no treatment-related non-neoplastic liver lesions in males and a decrease in basophilic cytological change reported from TCE-exposure in female rats. **The results for detecting a carcinogenic response in rats were considered to be equivocal because both groups receiving TCE showed significantly reduced survival compared to vehicle controls and because of a high rate (e.g., 20% of the animals in the high-dose group) of death by gavage error [emphasis added].**

Note well, however, that NTP (1990) is the same study in which the sole statistically significant finding of kidney cancer in rats was made by EPA (page 4-179, Table 4-41). Thus, EPA appears to accept the findings of NTP (1990) when the result is positive (kidney), but not when the result is negative (liver).

EPA then continues on page 4-399 with:

“In summary, overall there is limited available data in animals on the role of TCE in lymphomas and leukemias. There are few studies that analyze for lymphomas and/or leukemias. Lymphomas were described in four studies (NTP, 1990; NCI, 1976; Henschler et al., 1980, 1984) but study limitations (high background rate) in most studies make it difficult to determine if these are TCE-induced. Three studies found positive trends in leukemia in specific strains and/or gender (Maltoni et al., 1986, 1988; NTP, 1988). Due to study limitations, these trends cannot be determined to be TCE-induced.”

In reading the text between these two apparently disparate quotes, the data for these cancers is overwhelmingly negative; some data might be statistically significant negative (Henschler et al., 1984). The use of EPA (2005) would suggest that these experimental animals findings are negative.

As currently written, the best argument that EPA can make with these experimental animal data is that the data provide **suggestive evidence of carcinogenicity**. A holistic viewpoint, one that EPA espouses, limits the interpretation and reliability of the animal data, and/or decreases the weight of evidence for carcinogenicity in rodents. Based on these considerations, the animal data for these four tumors do not meet the criterion of “extensive evidence of carcinogenicity in animals.” Multiple marginal findings do not constitute “extensive evidence.” We encourage EPA to either revise its text, with appropriate supporting data, to support a judgment of “likely to cause cancer in humans,” or reconsider its conclusion based on these experimental animal data.

The epidemiologic literature on TCE can be characterized by many of the terms used to describe characteristics of the “suggestive” descriptor. These include the findings of a small increase in risk of tumors (kidney, NHL, liver) combined with the possibility that these cancers can be attributable to other known and unknown factors, and where there are studies that report positive responses, the limitations in study power, design, or conduct limit the ability to draw

“confident” conclusions. As shown in the data extracted from IRIS and presented in Table 11, the epidemiological data supporting a conclusion of “known” human carcinogen, or “A carcinogen” for other chemicals under the 1986 guidelines, is typically much stronger than the data for TCE.

The available experimental animal evidence can be interpreted in various ways depending on how EPA chooses to revise its text. As currently written, this evidence is primarily negative or conflicting for kidney and immune tumors, and positive for mouse liver tumors and lung tumors, and thus the overall weight of evidence considering both epidemiology and experimental animal evidence would be best seen as “suggestive.” However, a more complete presentation and analysis of the animal data may push the overall classification into the “likely” category based on a “suggestive” characterization of the epidemiologic literature and consideration of the weight of evidence from the animal tumor data, particularly the data on liver tumors in mice.

However, in no circumstance is it scientifically reasonable to judge that TCE is “carcinogenic to humans” based on the available human and experimental animal data.

In summary, a review of the available epidemiologic evidence and related meta-analyses, and the experimental animal data as presented in the document indicate “**suggestive evidence of carcinogenic potential**” of TCE based on the EPA cancer guidelines. The overall database may indicate that TCE is at the low end of “likely human carcinogen,” but the document as written does not currently make that case. Description of TCE as a known human carcinogen is precluded by:

- Methodological and analytical inconsistencies in the epidemiologic literature, such as weak summary associations, differences in results by sub-groups, lack of evidence of

dose-response relationships or insufficient data to fully evaluate exposure trends, and the potential influence of confounding by lifestyle or occupational factors.

Description of TCE as a likely carcinogen based on the draft EPA text is:

- Downweighted by the conflicting or negative experimental animal data for kidney and immune tumors, and weakly supported by the positive findings for mouse liver and lung tumors.
- EPA could improve its determination of kidney tumors findings by conducting a complete historical control analysis for each study that it deems scientifically credible, but it will need to re-evaluate NTP 1990 to determine whether this study meets these criteria. EPA should not discount the negative findings for NTP (1990) for rat liver tumors, but then accept the same study for findings of rat kidney tumors.<sup>2</sup>

## References

Alexander DD, Kelsh MA, Mink PJ, Mandel JH, Basu R, Weingart W. A meta-analysis of occupational trichloroethylene exposure and liver cancer. *Int Arch Occup Environ Health* 2007; 81(2):127–143.

Alexander DD, Mink PJ, Mandel JH, Kelsh MA. A meta-analysis of occupational trichloroethylene exposure and multiple myeloma or leukemia. *Occup Med* 2006; 56(7):485–93.

Charbotel B, Fevotte J, Hours M, Martin J, Beregeret A. Case-Control Study on Renal Cell Cancer and Occupational Exposure to Trichloroethylene. Part II: Epidemiological Aspects. *Ann.Occup.Hyg.* 2006.

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Raaschou-Nielsen O et al. Cancer risk among workers at Danish companies using trichloroethylene: a cohort study. *Am.J.Epidemiol.* 2003;158:1182-92.

U.S. Environmental Protection Agency. 2005. Guidelines for carcinogen risk assessment. Washington D.C. EPA/630/P-03/001B.

Table 11. Summary of the Number of Positive and Negative Studies for “Known” or “A” Human Carcinogens

Chemical (Year of Assessment)	Epi Positive <sup>1</sup>	Epi Negative <sup>2</sup>	Animal Positive	Animal Negative	Rare <sup>3</sup>
Arsenic, inorganic (1994)	14	ND	1	4	N
Asbestos (1987)	7(9)	1	3	3	Y (mesothelioma)
Benzene (1998)	5(11) <sup>4</sup>	ND	- <sup>4</sup>	-	N
Benzene (2000 oral)	- <sup>4</sup>	-	4(9)	ND	N
Benzene (1998 inhalation)	-	-	3(5)	ND	N
Benzidine (1986)	5	ND	1	4	N
Bis (chloromethyl) ether (BCME) (1988)	6	ND	1	4	N
Chloromethyl methyl ether (CMME) (1987)	9	ND	3	4	N
Chromium (VI) (1998)	25(30)	ND	5	8	Y
Coke oven emissions (1989)	6(8)	2	2	2	Y
Nickel Refinery Dust (1987)	6	ND	1	9	N
Nickel subsulfide (1987)	5	1	2	4	Y

Vinyl Chloride (2000)	11(16)	2	8(10)	6(8)	Y (angio- sarcoma)
1,3-Butadiene (2001)	7(9)	ND	1	1	N

<sup>1</sup> First number is the best estimate of number of unique cohorts, based on the IRIS summary. The number in parentheses is total number of citations of studies.

<sup>2</sup> ND = not determinable from writeup; no studies were mentioned, but it is not clear from the writeup whether negative studies exist, but were not included because a strength of evidence approach was in use at the time.

<sup>3</sup> Tumor associated with the chemical exposure has a very low background in humans, increasing the specificity of the association.

<sup>4</sup> There is one IRIS assessment for benzene, with portions from 1998 and 2000. The human data are presented in the initial 1998 assessment, while inhalation data for animals were presented in the 1998 document, and oral animal data presented in a 2000 document.

Table 1. **Percentage** of kidney adenoma (A) or carcinoma (C) in rats of various long-term **ORAL** bioassays

Dose (mg/kg)	Male		Female		Route	Strain	Duration	Reference		
	A	C	A	C						
0	0	0	0	0	Gavage	F344/N	103-wk	NTP (1990)		
0	0	0	0	0	Gavage	ACI	2-yr	NTP (1988)	<u>Total dose groups</u>	74
0	0	0	0	0	Gavage	Osborn-Mendel	2-yr	NCI (1976)	expected statistically significant	4
0	0	0	2	0	Gavage	August	2-yr	NTP (1988)	observed biologically significant	6
0	0	0	2	0	Gavage	Marshall	2-yr	NTP (1988)		
0	0	0	0	0	Gavage	Osborne-Mendel	2-yr	NTP (1988)	<u>High dose groups</u>	34
0	0	0	0	0	Gavage	Swiss	89-wk	Van Duuren et al., 1979	expected statistically significant	2
									observed biologically significant at high dose	1
500	12	0	0	0	Gavage	Osborne-Mendel	2-yr	NTP (1988)		
500	2	0	2	2	Gavage	Marshall	2-yr	NTP (1988)	Yellow highlight indicates judgment of biological significance.	
500	2	2	4	4	Gavage	August	2-yr	NTP (1988)		
500	0	2	4	2	Gavage	ACI	2-yr	NTP (1988)		
500	4	0	0	0	Gavage	F344/N	103-wk	NTP (1990)		
549	0	2	0	0	Gavage	Osborn-Mendel	2-yr	NCI (1976)		
1000	2	2	2	0	Gavage	Osborne-Mendel	2-yr	NTP (1988)		
1000	0	2	0	2	Gavage	Marshall	2-yr	NTP (1988)		
1000	2	0	0	0	Gavage	August	2-yr	NTP (1988)		
1000	0	0	0	2	Gavage	ACI	2-yr	NTP (1988)		
1000	0	6	0	2	Gavage	F344/N	103-wk	NTP (1990)		
1097	0	0	0	0	Gavage	Osborn-Mendel	2-yr	NCI (1976)		

Table 2. **Percentage** of kidney adenoma (A) or carcinoma (C) in rats of various long-term **INHALATION** bioassays

Dose (ppm)	Male		Female		Route	Strain	Duration	Reference
	A	C	A	C				
0	0	0	0	0	Inhalation	Sprague-Dawley	2-yr	Maltoni et al. (1988)
0	7	0	0	0	Inhalation	Han:WIST	18-mo	Henschler et al., 1980
0	-	-	0	0	Inhalation	Crj:CD (SD)	2-yr	Fukuda et al., 1983
50	-	-	0	0	Inhalation	Crj:CD (SD)	2-yr	Fukuda et al., 1983
100	1	0	1	0	Inhalation	Sprague-Dawley	2-yr	Maltoni et al. (1988)
100	3	0	0	0	Inhalation	Han:WIST	18-mo	Henschler et al., 1980
150	-	-	0	0	Inhalation	Crj:CD (SD)	2-yr	Fukuda et al., 1983
300	0	0	0	0	Inhalation	Sprague-Dawley	2-yr	Maltoni et al. (1988)
450	-	-	0	2	Inhalation	Crj:CD (SD)	2-yr	Fukuda et al., 1983
500	7	3	3	0	Inhalation	Han:WIST	18-mo	Henschler et al., 1980

600 | 1 3 0 1 Inhalation Sprague-Dawley 2-yr Maltoni et al. (1988)

"-" = No data

Table 3. **Percentage** of liver adenoma (A) or carcinoma (C) in rats of various long-term **ORAL** bioassays

Dose (mg/kg)	Male		Female		Route	Strain	Duration	Reference		
	A	C	A	C						
0	-	0	-	0	Gavage	F344/N	103-wk	NTP (1990)		
0	-	0	-	0	Gavage	Osborn-Mendel	2-yr	NCI (1976)		
0	0	2	0	0	Gavage	ACI	2-yr	NTP (1988)		
0	0	0	0	4	Gavage	August	2-yr	NTP (1988)	<u>Total dose groups</u>	54
0	2	2	0	0	Gavage	Marshall	2-yr	NTP (1988)	expected statistically significant	3
0	2	2	0	0	Gavage	Osborne-Mendel	2-yr	NTP (1988)	observed biologically significant	1
500	-	0	-	2	Gavage	F344/N	103-wk	NTP (1990)	<u>High dose groups</u>	26
500	0	2	0	0	Gavage	ACI	2-yr	NTP (1988)	expected statistically significant	1
500	0	2	0	0	Gavage	August	2-yr	NTP (1988)	observed biologically significant at high dose	1
500	0	0	0	0	Gavage	Marshall	2-yr	NTP (1988)		
500	2	0	0	4	Gavage	Osborne-Mendel	2-yr	NTP (1988)		
549	-	0	-	2	Gavage	Osborn-Mendel	2-yr	NCI (1976)		
1000	-	2	-	2	Gavage	F344/N	103-wk	NTP (1990)		
1000	0	2	0	0	Gavage	August	2-yr	NTP (1988)		
1000	0	2	0	0	Gavage	ACI	2-yr	NTP (1988)		
1000	0	2	0	0	Gavage	Marshall	2-yr	NTP (1988)		
1000	2	4	0	4	Gavage	Osborne-Mendel	2-yr	NTP (1988)		
1097	-	0	-	0	Gavage	Osborn-Mendel	2-yr	NCI (1976)		

Yellow highlight indicates judgment of biological significance.

Table 4. **Percentage** of liver adenoma (A) or carcinoma (C) in rats of various long-term **INHALATION** bioassays

Dose (ppm)	Male		Female		Route	Strain	Duration	Reference
	A	C	A	C				
0	3	0	0	0	Inhalation	Han:WIST	18-mo	Henschler et al. (1980)
0	-	-	0	0	Inhalation	Crj:CD (SD)		Fukuda et al., 1983
50	-	-	2	0	Inhalation	Crj:CD (SD)		Fukuda et al., 1983
100	3	0	3	3	Inhalation	Han:WIST	18-mo	Henschler et al. (1980)
150	-	-	0	0	Inhalation	Crj:CD (SD)		Fukuda et al., 1983
400	-	-	0	2	Inhalation	Crj:CD (SD)		Fukuda et al., 1983
500	0	0	7	0	Inhalation	Han:WIST	18-mo	Henschler et al. (1980)

|

"-" = No data

Table 5. **Percentage** of liver adenoma (A) or carcinoma (C) in mice of various long-term **ORAL** bioassays

Dose (mg/kg)	Male		Female		Route	Strain	Duration	Reference		
	A	C	A	C						
0	15	17	8	4	Gavage	B6C3F1	103-wk	NTP (1990)	<u>Total dose groups</u>	34
0	-	5	-	0	Gavage	B6C3F1	2-yr	NCI (1976)	expected statistically significant	2
0	10	0	2	0	Gavage	Swiss	18-mo	Henschler et al., 1984	observed biologically significant	12
869	-	-	-	8	Gavage	B6C3F1	2-yr	NCI (1976)		
1000	28	62	33	27	Gavage	B6C3F1	103-wk	NTP (1990)	<u>High dose groups</u>	18
1169	-	52	-	-	Gavage	B6C3F1	2-yr	NCI (1976)	expected statistically significant	1
1739	-	-	-	23	Gavage	B6C3F1	2-yr	NCI (1976)	observed biologically significant at high dose	10
2339	-	65	-	-	Gavage	B6C3F1	2-yr	NCI (1976)		

Yellow highlight indicates judgment of biological significance.

Table 6. **Percentage** of liver adenoma (A) or carcinoma (C) in mice of various long-term **INHALATION** bioassays

Dose (ppm)	Male		Female		Route	Strain	Duration	Reference	
	A	C	A	C					
0	-	4	-	0	Inhalation	Swiss	78-wk	Maltoni et al. (1988)	Hepatoma?
0	-	1	-	3	Inhalation	B6C3F1	78-wk	Maltoni et al. (1988)	Hepatoma?
0	3	3	0	0	Inhalation	Han:NMRI	18-mo	Henschler et al., 1980	
0	-	-	0	0	Inhalation	Crj:CD (ICR)	2-yr	Fukuda et al., 1983	
50	-	-	0	0	Inhalation	Crj:CD (ICR)	2-yr	Fukuda et al., 1983	
100	-	1	-	4	Inhalation	B6C3F1	78-wk	Maltoni et al. (1988)	Hepatoma?
100	-	2	-	0	Inhalation	Swiss	78-wk	Maltoni et al. (1988)	Hepatoma?
100	7	0	0	0	Inhalation	Han:NMRI	18-mo	Henschler et al., 1980	
150	-	-	0	0	Inhalation	Crj:CD (ICR)	2-yr	Fukuda et al., 1983	
300	-	3	-	4	Inhalation	B6C3F1	78-wk	Maltoni et al. (1988)	Hepatoma?
300	-	9	-	0	Inhalation	Swiss	78-wk	Maltoni et al. (1988)	Hepatoma?
450	-	-	2	0	Inhalation	Crj:CD (ICR)	2-yr	Fukuda et al., 1983	
500	0	0	0	0	Inhalation	Han:NMRI	18-mo	Henschler et al., 1980	
600	-	14	-	1	Inhalation	Swiss	78-wk	Maltoni et al. (1988)	Hepatoma?
600	-	7	-	10	Inhalation	B6C3F1	78-wk	Maltoni et al. (1988)	Hepatoma?

Table 7. **Percentage** of pulmonary adenoma (A) or carcinoma (C) in rats of various long-term **ORAL** bioassays

Dose (mg/kg)	Male		Female		Route	Strain	Duration	Reference
	A	C	A	C				
0	5	0	0	0	Gavage	Osborne-Mendel	78-wk	NCI, 1976
0	2	2	0	0	Gavage	ACI	103-wk	NTP, 1988
0	2	0	2	2	Gavage	August	103-wk	NTP, 1988
0	6	6	6	6	Gavage	Marshall	103-wk	NTP, 1988
0	4	2	0	0	Gavage	Osborne-Mendel	103-wk	NTP, 1988
0	8	6	2	0	Gavage	F344	103-wk	NTP, 1990
0	0	0	0	0	Gavage	S-D	56-wk	Maltoni et al. 1986
50	0	0	0	0	Gavage	S-D	56-wk	Maltoni et al. 1986
250	0	0	0	0	Gavage	S-D	56-wk	Maltoni et al. 1986
500	9	4	4	2	Gavage	ACI	103-wk	NTP, 1988
500	2	2	2	0	Gavage	August	103-wk	NTP, 1988
500	4	4	6	6	Gavage	Marshall	103-wk	NTP, 1988
500	2	2	6	6	Gavage	Osborne-Mendel	103-wk	NTP, 1988
500	4	4	2	0	Gavage	F344	103-wk	NTP, 1990
549	0	0	2	2	Gavage	Osborne-Mendel	78-wk	NCI, 1976
1000	0	0	5	5	Gavage	ACI	103-wk	NTP, 1988
1000	0	0	0	0	Gavage	August	103-wk	NTP, 1988
1000	4	4	2	2	Gavage	Marshall	103-wk	NTP, 1988
1000	2	0	4	2	Gavage	Osborne-Mendel	103-wk	NTP, 1988
1000	6	6	8	4	Gavage	F344	103-wk	NTP, 1990
1097	0	0	0	0	Gavage	Osborne-Mendel	78-wk	NCI, 1976

<u>Total dose groups</u>	82
expected statistically significant	4
observed biologically significant	1
<u>High dose groups</u>	58
expected statistically significant	3
observed biologically significant at high dose	1

Yellow highlight indicates judgment of biological significance.

Table 8. **Percentage** of pulmonary adenoma (A) or carcinoma (C) in rats of various long-term **INHALATION** bioassays

Dose (ppm)	Male		Female		Route	Strain	Duration	Reference
	A	C	A	C				
0	-	-	0	0	Inhalation	S-D	104-wk	Fukuda et al. 1983
0	0	0	0	0	Inhalation	S-D	104-wk	Maltoni et al. 1986, 1988
0	3	3	0	0	Inhalation	Wistar	78-wk	Henschler et al. 1980
50	-	-	0	0	Inhalation	S-D	104-wk	Fukuda et al. 1983
100	3	3	3	3	Inhalation	Wistar	78-wk	Henschler et al. 1980
100	0	0	0	0	Inhalation	S-D	104-wk	Maltoni et al. 1986, 1988
150	-	-	2	0	Inhalation	S-D	104-wk	Fukuda et al. 1983
300	0	0	0	0	Inhalation	S-D	104-wk	Maltoni et al. 1986, 1988
450	-	-	2	0	Inhalation	S-D	104-wk	Fukuda et al. 1983
500	3	3	0	0	Inhalation	Wistar	78-wk	Henschler et al. 1980
600	0	0	0	0	Inhalation	S-D	104-wk	Maltoni et al. 1986, 1988



"-" = No data

Table 9. **Percentage** of pulmonary adenoma (A) or carcinoma (C) in mice of various long-term **ORAL** bioassays

Dose (mg/kg)	Male		Female		Route	Strain	Duration	Reference		
	A+C	C	A+C	C						
0	36	16	24	10	Gavage	Swiss	72-wk	Henschler et al. 1984	<u>Total dose groups</u>	70
0	0	0	0	0	Gavage	Swiss	89-wk	Van Duuren et al. 1979	expected statistically significant	4
0	0	5	0	0	Gavage	B6C3F1	78-wk	NCI, 1976	observed biologically significant	14
0	14	6	2	2	Gavage	B6C3F1	103-wk	NTP 1990		
869	-	-	8	4	Gavage	B6C3F1	78-wk	NCI, 1976	<u>High dose groups</u>	46
1000	12	6	8	0	Gavage	B6C3F1	103-wk	NTP 1990	expected biologically significant	2
1169	10	0	-	-	Gavage	B6C3F1	78-wk	NCI, 1976	observed biologically significant at high dose	10
1739	-	-	15	4	Gavage	B6C3F1	78-wk	NCI, 1976		
1800	-	-	40	22	Gavage	Swiss	72-wk	Henschler et al. 1984		
1800	-	-	42	16	Gavage	Swiss	72-wk	Henschler et al. 1984		
1800	-	-	34	6	Gavage	Swiss	72-wk	Henschler et al. 1984		
1800	-	-	36	14	Gavage	Swiss	72-wk	Henschler et al. 1984		
1800	-	-	36	14	Gavage	Swiss	72-wk	Henschler et al. 1984		
2339	4	2	-	-	Gavage	B6C3F1	78-wk	NCI, 1976		
2400	34	12	-	-	Gavage	Swiss	72-wk	Henschler et al. 1984		
2400	28	14	-	-	Gavage	Swiss	72-wk	Henschler et al. 1984		
2400	42	10	-	-	Gavage	Swiss	72-wk	Henschler et al. 1984		
2400	30	14	-	-	Gavage	Swiss	72-wk	Henschler et al. 1984		
2400	36	14	-	-	Gavage	Swiss	72-wk	Henschler et al. 1984		

Yellow highlight indicates judgment of biological significance.

Table 10. **Percentage** of pulmonary adenoma (A) or carcinoma (C) in mice of various long-term **INHALATION** bioassays

Dose (ppm)	Male		Female		Route	Strain	Duration	Reference
	A+C	C	A+C	C				
0	-	-	12	2	Inhalation	ICR	104-wk	Fukuda et al. 1983
0	11	0	17	2	Inhalation	Swiss	104-wk	Maltoni et al. 1986, 1988
0	2	0	4	0	Inhalation	B6C3F1	104-wk	Maltoni et al. 1986, 1988
0	3	17	10	3	Inhalation	NMRI	78-wk	Henschler et al. 1980
50	-	-	10	6	Inhalation	ICR	104-wk	Fukuda et al. 1983
100	12	0	17	0	Inhalation	Swiss	104-wk	Maltoni et al. 1986, 1988
100	2	0	7	1	Inhalation	B6C3F1	104-wk	Maltoni et al. 1986, 1988
100	10	10	0	10	Inhalation	NMRI	78-wk	Henschler et al. 1980
150	-	-	26	16	Inhalation	ICR	104-wk	Fukuda et al. 1983
300	26	0	14	0	Inhalation	Swiss	104-wk	Maltoni et al. 1986, 1988
300	3	0	8	0	Inhalation	B6C3F1	104-wk	Maltoni et al. 1986, 1988
450	-	-	24	15	Inhalation	ICR	104-wk	Fukuda et al. 1983
500	3	3	4	0	Inhalation	NMRI	78-wk	Henschler et al. 1980
600	1	0	17	0	Inhalation	B6C3F1	104-wk	Maltoni et al. 1986, 1988
600	30	1	22	2	Inhalation	Swiss	104-wk	Maltoni et al. 1986, 1988



"-" = No data