

AUG 18 1987

MEMORANDUM

OFFICE OF  
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Peer Review of Para-Dichlorobenzene (PDCB)

FROM: John A. Quest, Ph.D.  
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TO: Barbara Mandula (TS-788)  
Karl Baetcke, Ph.D. (TS-796)  
Larry Anderson, Ph.D. (WH-550D)  
William Farland, Ph.D. (RD-689)

The Toxicology Branch Peer Review Committee met on January 29, 1987 to review the toxicology data base on PDCB. Attention was focused on the oncogenic potential of the chemical in rats and mice.

A. Individuals in Attendance

1. Peer Review Committee: (Signature indicates concurrence with the peer review unless otherwise stated.)

Anne Barton

Diane Beal

Robert Beliles

William Burnam

Keto Engler

Theodore M. Farber

Judith Hauswirth

Richard Hill

Louis Kasza

Richard Levy

*John A. Quest*  
*Diane Beal*  
*Robert Beliles*  
*William Burnam*  
*Keto Engler*  
*Theodore M. Farber*  
*Judith W. Hauswirth*  
*Richard Hill*  
*Louis Kasza*  
*Richard Levy*

John A. Quest

John A. Quest

Esther Rinde

Esther Rinde

2. Scientific Reviewers: (Noncommittee members responsible for presentation of data; signature indicates technical accuracy of panel report.)

Karl Baetcke

Karl Baetcke

Barbara Mandula

Barbara Mandula

3. Other Attendees: The following individuals from the Office of Toxic Substances (OTS) the Office of Drinking Water (ODW) and the Office of Pesticide Programs (OPP) attended the peer review meeting: Larry Anderson, Albin Kocialski, Frank Kover, C.J. Nelson, Bill Pepelko, Jeanette Wiltse, and Robert Zendzian.

B. Material Reviewed

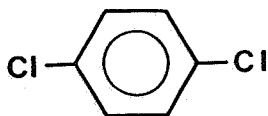
The material reviewed consisted of background toxicology memoranda on PDCB developed by OTS. These were: (1) Review of NTP Studies on Paradichlorobenzene for Evidence that MTD's were Exceeded, January 5, 1987 (K.P. Baetcke to B. Mandula); (2) Review of Inhalation Studies Performed on Paradichlorobenzene by ICI, December 8, 1986 (K.P. Baetcke to B. Mandula); (3) Assessment of Human Cancer Risks from Para-Dichlorobenzene, January 5, 1987 (B. Mandula, K. Baetcke, D. Beal, C.J. Nelson, V. Rodriguez, and G. Thom); and (4) Questions on Paradichlorobenzene Risk Assessment, December 31, 1986 (J.A. Wiltse to T.M. Farber).

C. Background Information

PDCB is a high production halogenated hydrocarbon chemical (approximately 18 million kilograms were used in 1986) that has both pesticidal and industrial uses. It is used as a water contact (i.e., toilet) deodorant, an air deodorant, a moth repellent, and as an intermediate in the production of engineering plastics and dyes. There are three major categories of human exposure, namely consumer, occupational, and ambient air and water. The major route of exposure to the general public and to workers is via inhalation, whereas exposure from drinking water is much lower than from inhalation.

PDCB is currently being evaluated by both OTS and OPP, primarily on the basis of oncogenicity studies that have been performed by the National Toxicology Program (NTP) in rats and mice, using the oral route of administration (gavage in corn oil), and by Imperial Chemical Industries (ICI) in both rodent species, using the inhalation route of administration. The NTP studies described positive tumor findings in male rats (kidney tumors) and in male and female mice (liver tumors), whereas the ICI studies were negative for oncogenic effects. (The ICI study in mice was inadequate and thus unacceptable for oncogenicity evaluation purposes). An initial evaluation of the above as well as other available toxicological information by OTS scientists led to the conclusion that PDCB could be classified as a Category B2 carcinogen, with the recognition that a Category C classification might also be supportable based upon arguments about the relevance of male rat kidney and mouse liver tumors, produced by oral administration of PDCB in corn oil vehicle, to the human situation where inhalation exposure is paramount. In view of this difficulty in classifying PDCB as to oncogenic category, and because the chemical has both industrial and pesticidal uses, the present meeting was convened to discuss the weight of the evidence of PDCB in the presence of both OTS and OPP representatives.

Structure:



para-dichlorobenzene  
(1,4-dichlorobenzene)

D. Evaluation of Oncogenicity Studies

1. NTP Rat Oncogenicity Study: PDCB was administered by gavage in corn oil vehicle to groups of 50 male and 50 female F344/N rats at doses of 0, 150, and 300 mg/kg/day (male rats) or 0, 300, and 600 mg/kg/day (female rats) for 5 days/week for 104 weeks. The incidence pattern of tumors that were described in the kidney of male rats are summarized below in tabular form. No significant increases in tumors were observed in female rats.

Kidney Tumor Type	Dose (mg/kg/day)			Historical Controls <sup>b/</sup>	
	0	150	300	Test Lab	NTP
Tubular Cell:					
Adenoma	0/50 (0%)	0/50 (0%)	1/50 (2%)	0%	0.1%
Adenocarcinoma	1/50 (2%)	3/50 (6%)	7/50 (14%) <sup>a/</sup>	0%	0.4%
Combined	1/50 (2%)	3/50 (6%)	8/50 (16%) <sup>a/</sup>	0.7%	0.5%

a/ p < 0.05 compared to concurrent controls.

b/ Average values (%) from test laboratory (Battelle) and from all NTP studies; no range information was available.

Renal tubular cell adenocarcinomas, and adenomas and adenocarcinomas combined, were significantly elevated in male rats at the highest dose level tested. The increased tumorigenic responses seen at the highest dose level also exceeded the average historical control incidences for similar tumors obtained both in studies at the test laboratory and in all NTP studies overall (see above table). Evidence to support a reduced latency period for adenocarcinoma development in the high dose animals was also present (i.e., the first adenocarcinoma in the high dose group occurred at treatment week 46, and the second and third occurred at treatment weeks 90 and 98, respectively, whereas these tumors were first observed at 104 weeks and 101 weeks in the control and low dose groups, respectively). An increased incidence of renal tubular cell hyperplasia was also observed in high dose male rats (9/50 vs. 0/50 and 1/50 in control and low dose groups, respectively).

The following signs of generalized toxicity and non-neoplastic pathology changes occurred in male rats: (a) decreased survival at the high dose level (26/50 or 52% died by termination of the study vs. 11/50 or 22% in controls); (b) reduced body weight gain at the high dose level (-5% to -8%); (c) renal mineralization at both dose levels tested (4/50, 8%, minimal severity, controls; 46/50, 92%, mild to moderate severity, low dose; 47/50, 94%, moderate to high severity, high dose); and (4) renal pelvic hyperplasia at both dose levels tested (1/50, 2%, controls; 30/50, 60%, low dose; 31/50, 62%, high dose). The above-cited decreased survival rate in high dose male rats did not become significantly different from control animals until study week 97, a time when tumors had already appeared in most treated animals. In addition, many of the high dose males that died had leukemia thereby raising the question of whether this lesion was the cause of death. The

Committee discussed the above information in some detail, but was unable to agree on whether or not a maximum tolerated dose (MTD) level was reached. Some members argued that the high dose level approximated a MTD level according to NTP's criteria by inducing non-life-threatening pathologic effects. Others, however, argued that the severity of some of the effects (e.g., mineralization) resulted in the high dose level being over the MTD level and that this dose was inadequate for accurately predicting an oncogenic response.

Information was provided on a possible mechanism for the formation of the renal tumors, which has been hypothesized to be specific and unique to male rats. According to data developed by the Chemical Industry Institute of Toxicology (CIIT), the male rat kidney is susceptible to induction of tumors by some organic compounds (e.g., unleaded gasoline, PDCB, etc.) because it contains alpha-2u-globulin, a protein that is under androgenic control and not present, or present only in very low levels, in female rat kidneys, mice, and humans. Chemicals such as PDCB have been shown to cause an increase in hyaline droplets (composed of alpha-2u-globulin) in the proximal convoluted tubules of male rats leading to renal cell damage. It is postulated that this process results in increased cell proliferation and opportunities for genetic events to occur that can lead to tumor formation. Of concern to the Committee was the relevance of this mechanism to the human situation. Some members felt that not enough information was available at the present time to rule out possible risks to man whereas others thought that information was suggestive of a nonrisk situation to humans.

2. NTP Mouse Oncogenicity: PDCB was administered by gavage in corn oil vehicle to groups of 50 male and 50 female B6C3F<sub>1</sub> mice at doses of 0, 300, and 600 mg/kg/day for 5 days/week for 104 weeks. The following incidence patterns of liver tumors suggestive of a compound-related effect were observed in male and female mice.

Liver Tumor Type	Sex	Dose (mg/kg/day)		
		0	300	600
Adenoma	M	5/50 (10%)	12/49 (24%)	16/50 (32%) <sup>a/</sup>
Carcinoma	M	14/50 (28%)	11/49 (22%)	32/50 (64%) <sup>a/</sup>
Combined	M	17/50 (34%)	22/49 (45%)	40/50 (80%) <sup>a/</sup>
Hepatoblastoma <sup>b/</sup>	M	0/50 (0%)	0/49 (0%)	4/50 (8%)

Liver Tumor Type	Sex	Dose (mg/kg/day)		
		0	300	600
Adenoma	F	10/50 (20%)	6/48 (13%)	21/50 (42%) <sup>a/</sup>
Carcinoma	F	5/50 (10%)	5/48 (10%)	19/50 (38%) <sup>a/</sup>
Combined	F	15/50 (30%)	10/48 (21%)	36/50 (72%) <sup>a/</sup>

a/ p < 0.05 compared to controls.

b/ All hepatoblastomas were observed in animals also bearing hepatocellular carcinomas.

Hepatocellular adenomas, carcinomas, and adenomas plus carcinomas combined were significantly elevated in male and female mice at the highest dose level tested. In addition, there were significant positive trends for all three categories of tumors in both sexes of mice. Among the hepatocellular carcinomas that were seen in the high dose males were four hepatoblastomas, a more uncommon and malignant type of liver tumor than hepatocellular carcinoma. Neither liver hyperplasia nor a reduction in the latency period to tumor development occurred in male or female mice. Historical control data have been provided for liver tumors in B6C3F<sub>1</sub> mice by the NTP (Toxicologic Pathol. 12:126-135, 1984; Handbook of Carcinogen Testing, Noyes Pubs., N.J. p. 291, 1984). In male mice, historical control rates were: adenoma (10.3%, range 0-24%); carcinoma (21.3%; range 8-36%); combined (31.1%, range 16-58). In female mice, historical control rates were: adenoma (4.0%, range 0-18%); carcinoma (4.1%, range 0-15%); combined (7.9%, range 0-20%). Comparison of these data with those in the above table indicates that the following liver tumors were outside of the historical control ranges: (1) adenomas, carcinomas, and adenomas/carcinomas combined in high dose male and high dose female mice; and (2) concurrent control incidences of adenomas, and adenomas/carcinomas combined, in female mice. In addition, the incidence of hepatoblastomas in high dose male mice exceeded the NTP historical control incidence (0/3500 or 0%).

In terms of general toxic effects, PCB-treated mice exhibited no increase in mortality and no reduction in body weight gain compared to control animals. The following non-neoplastic pathology changes occurred at the mid and high dose levels in both male and female mice: (a) nephropathy (males, 12% controls, 24% low dose, 32% high dose; females, 0% controls, 6% low dose, 7% high dose); (b) hepatocellular degeneration

(males, 0% controls, 73% low dose, 78% high dose; females, 0% controls, 17% low dose, 72% high dose); (c) liver focal necrosis (males, 2% controls, 71% low dose, 74% high dose; females, 2% controls, 8% low dose, 60% high dose); and (d) liver cell size alteration (males, 0% controls, 78% low dose, 80% high dose; females 0% controls, 8% low dose, 54% high dose). The Committee had divergent opinions as to whether the above changes met or exceeded an MTD level. Some individuals felt that an MTD level was not exceeded since the above changes were mildly severe in nature (e.g., the liver necrosis involved single cells only and was minimum to mild in severity). In contrast, others believed that they were sufficiently severe to indicate that the MTD level was exceeded.

The relevance of the mouse liver tumors to the human risk situation was discussed. Factors considered to strengthen the case for the significance of the mouse response were: (a) benign tumors were not the predominant response observed; males had more carcinomas than adenomas, and females had an equivalent number of carcinomas compared to adenomas; (b) significant increases in tumors were found in both sexes at the high dose level, and the elevated tumor incidences were relatively great in magnitude; (c) hepatoblastomas, a rare and very malignant form of hepatocellular carcinoma occurred in high dose male mice; and (d) tumors in high dose animals exceeded historical control incidences. Factors considered to weaken the case for the significance of the mouse response were: (a) interpretation of excess liver tumors is uncertain because of the high background rates seen in control male and female mice (the incidences of adenomas in control females actually exceeded historical rates); (b) a statistically significant increase in tumors occurred only in the highest dose group in males and females, and only at the end of the study in almost all animals; (c) there was no dose-related increase in the proportion of malignant (vs. benign plus malignant) tumors in either sex; (d) no reduction in the time to tumor appearance was seen; and (e) not much support for a positive oncogenic response was obtained from genetic toxicology tests or structure-activity comparisons (see below).

3. ICI Rat and Mouse Oncogenicity Studies: PCB was administered via the inhalation route of exposure to groups of 76 to 79 Alderley Park Wistar-derived rats and 75 SPF Swiss mice of both sexes at concentrations of 0, 75, and 500 ppm in air for 5 hours/day, 5 days/week. Rats were exposed for 76 weeks and surviving

animals observed until 108- to 112 weeks. Mice were exposed for 57 weeks and surviving animals observed for another 19 weeks. In the rat study, no statistically significant increase in tumors was observed in treated animals compared to controls. In the mouse study, limitations regarding insufficient histopathological evaluation of tissues and respiratory infection precluded useful interpretation of the data.

Although the duration of dosing in the rat chronic study was relatively short (76 weeks), the Committee felt that overall it was a reasonably well designed study. This was the case even though the highest concentration level tested (500 ppm) was estimated to be below an MTD level. That is, the only toxicological change produced by this concentration of PDCB in rats was a slight increase in kidney weight. Data from other shorter term inhalation studies in rats however showed that a PDCB concentration of 1000 ppm was lethal. Thus, the high concentration of 500 ppm employed in the ICI chronic inhalation bioassay was at least 1/2 the MTD level and therefore would be acceptable to the OPP for the purpose of evaluating potential oncogenic activity of PDCB in rodents.

The Committee also discussed the issue of whether the concentrations of PDCB administered to rats in the ICI inhalation study were comparable to the doses administered to rats (i.e., 150 and 300 mg/kg/day) in the NTP gavage study. Mathematical analyses provided to the group using calculations of chamber air concentrations, respiratory minute volume, etc., plus data from a metabolism study in rats (Xenobiotica 10:81-95, 1980) indicated that the inhaled dose was lower than the higher dose in the gavage study. The dose rate delivered in the ICI study at 500 ppm was considered to roughly approximate that delivered in the NTP study at the 150 mg/kg/day dose level. Subsequent to evaluation of the information, the group felt that a firm basis did not really exist for comparison of the two routes of administration for two reasons. The first reason was that the metabolism study used to support the comparison had substantive deficiencies. It was performed in only two rats/dose group and only in female rats that were of a different strain from that used in the ICI study, the durations of inhalation and gavage exposure were short (up to 10 days), it could not be determined if the tissue concentrations of <sup>14</sup>C that were derived were from both or perhaps only one rat/dose group, and the animals were sacrificed 24 hours after dosing at which time peak tissue



$^{14}\text{C}$  levels after inhalation and gavage dosing would be different. Also, the actual inhalation exposure could have been lower than that calculated mathematically using the assumed physiological parameters (e.g., minute volume) because of factors such as reflex apnea that can be displayed by rodents in response to inhaled toxicants. The second reason was that gavage administration using corn oil may be an inappropriate oral route for comparison to the inhalation route. That is, administration by corn oil gavage delivers a high concentration bolus injection rapidly into the GI tract, resulting in absorption of chemical in lipophilic solution directly into the portal vein and the liver via a first-pass effect. In contrast, administration by inhalation exposure results in a more continuous delivery of toxicant to the lungs and pulmonary circulation. Transit through the pulmonary system could result in some enzymatic metabolism of the chemical. In addition, delivery through the pulmonary circulation, left atria and ventricle, and systemic arterial circulation would result in a diluted blood concentration of PDCB reaching the liver, kidney, and other organs. Thus, both the doses of PDCB and the time-course of delivery to body organs would differ by the two routes of administration. Another factor relating to corn oil per se is that this vehicle may directly affect hyaline droplet formation and cell proliferation (see Transcript of Proceedings of NTP Board of Scientific Counselors on PDCB Technical Report, Vol. 1, p. 102-103, March 26, 1986). In summary, for the above reasons, some members of the Peer Review Committee felt that the corn oil gavage and inhalation routes of administration were not comparable for dose comparison and tumor evaluation purposes with PDCB. As a corollary, and most importantly, it was also believed by some that the tumors produced in rodents by PDCB administered by gavage in corn oil in the NTP studies were not relevant to determining the oncogenic risk in humans where the primary route of exposure is by inhalation.

#### E. Additional Toxicology Data

1. Metabolism: The pharmacokinetic activity of PDCB was evaluated in a study in female adult CFY-Sprague-Dawley rats (Xenobiotica 10:81-95, 1980). Groups of two animals/dose received  $^{14}\text{C}$ -labeled PDCB at doses of 250 mg/kg/day either orally (gavage) or subcutaneously for up to 10 days, or via inhalation at a concentration of 1000 ppm 3 hours/day, for up

to 10 days. The results reported that similar tissue distribution, metabolism, and excretion patterns occurred for PDCB by all three routes of administration. Highest levels of radioactivity (RA) were found in fat followed by kidney, lung and liver, plasma, and muscle. Peak tissue concentrations occurred in about 6 days; by 8 hours after the last of the repeated doses both tissue and plasma levels declined and were largely undetectable after 5 days. Over 90 percent of the RA was excreted in the urine, and the same urinary metabolites were found by all three routes (a sulfate and a glucuronide conjugate of 2,5-dichlorophenol). As noted above (section D.3.), the Peer Review Committee enumerated several deficiencies in this metabolism study.

2. Mutagenicity: A variety of genotoxicity tests have been performed using PDCB and all have been reported negative. The chemical was not mutagenic in Salmonella nor in the mouse lymphoma test with or without metabolic activation, it did not induce unscheduled DNA synthesis in human lymphocytes in vitro, and did not increase sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells with or without metabolic activation. The Committee was aware of the fact that halogenated hydrocarbons, many of which are carcinogenic in animals, are often not genotoxic. One possible explanation for the negative mutagenicity results with Para-Dichlorobenzene and other carcinogenic chlorinated hydrocarbons is that the negative mutagenicity data supports the postulate that Para-Dichlorobenzene and other chlorinated hydrocarbons induce tumors in rodents by mechanisms not directly involving DNA damage, such as promotion.
3. Structure-Activity Considerations: Data from close structural analogues provided very limited support for the oncogenicity of PDCB. Information on three congeners is available. Orthodichlorobenzene was found to be negative for oncogenicity in F344 rats and B6C3F<sub>1</sub> mice. Monochlorobenzene produced neoplastic liver nodules in male F344 rats but no tumors in female rats or in B6C3F<sub>1</sub> mice of either sex (an MTD may not have been reached in these studies). Hexachlorobenzene was oncogenic in hamsters, rats, and mice.

#### F. Weight of Evidence Considerations

The Committee considered the following facts regarding toxicology data on PDCB to be of importance in a weight of the evidence determination of oncogenic potential.

1. PDCB was associated with a significantly elevated incidence of renal tubular cell adenocarcinomas, and adenocarcinomas and adenomas combined, at the highest dose level tested (300 mg/kg/day) following administration by gavage in corn oil vehicle in male F344 rats. The tumors occurred with a reduced latency period, occurred at incidences higher than average historical incidences for the same respective tumor types in F344/N male rats in NTP studies, and were accompanied by an elevated incidence of tubular cell hyperplasia. The NTP considered the male rat renal tumor finding to be "clear evidence" of carcinogenicity. No increased incidence of tumors occurred in female rats.
2. PDCB was associated with significantly elevated incidences of hepatocellular adenomas, carcinomas, and adenomas and carcinomas combined at the highest dose level tested (600 mg/kg/day) following administration by gavage in corn oil in male and female B6C3F<sub>1</sub> mice. The elevated incidences of these three tumor categories exceeded the historical control data ranges for the same respective tumor categories in male and female B6C3F<sub>1</sub> mice in NTP studies (as did also the concurrent control incidences of adenomas, and adenomas/carcinomas combined, in female mice). In addition, hepatoblastomas (a more uncommon and malignant tumor than hepatocellular carcinoma) were also seen in some of the high dose male mice that also bore hepatocellular carcinomas. Neither liver hyperplasia nor a reduction in the latency period to tumor development was observed in mice of either sex. The NTP considered the mouse live tumor findings to be "clear evidence" of carcinogenicity.
3. The Committee deliberated at length over the question of whether the highest dose levels tested in male rats (300 mg/kg/day) and in male and female mice (600 mg/kg/day) met or exceeded MTD levels in each respective study. Opinion was divided in each situation and no consensus agreement was reached (see sections D.1. and D.2. for discussions in rats and mice, respectively). In the case of individuals who believed that the MTD may have been exceeded, there was concern that the non-neoplastic pathology findings in both rats and mice may have contributed to the oncogenic responses that were observed. They further believed that the dose levels of PDCB causing these changes in rodents might not be seen with human exposure.
4. PDCB was not oncogenic when administered by inhalation to Alderley Park Wistar-derived rats at concentrations of 75 and 500 ppm, 5 hours/day, 5 days/week, for 76 weeks. With the exception of the shortened period of

compound-exposure in this study (EPA normally requires exposure for 104 weeks), it was generally considered to be adequate in design and conduct. Although the highest concentration level administered to rats did not exert much toxicity in treated animals, data from shorter term studies suggested that it was at least one-half a MTD level and therefore acceptable to the Agency as an adequate dose level for oncogenicity testing. A related inhalation study conducted in SPF Swiss mice at concentration levels of 75 and 500 ppm for 57 weeks was considered uninterpretable due to inadequate histopathology examinations and respiratory infections in the animals.

5. PCB was not found to be mutagenic in several genotoxicity assays. However the negative mutagenicity data may be an appropriate factor to weight in evaluating the significance of the male rat kidney tumors and the male and female mouse tumors observed in the NTP gavage studies.
6. Minimal support for the oncogenicity of PCB was provided from data on the closely related analogues ortho-dichlorobenzene (negative in rat and mouse studied) and monodichlorobenzene (produced neoplastic liver nodules in male rats but negative in female rats and in mice). Another less closely related chemical, hexachlorobenzene, was oncogenic in hamsters, mice, and rats.
7. Several major issues related to the oncogenicity studies of PCB were also discussed in detail by the Committee.
  - (a) The relevance of the kidney tumors in male rats was discussed. Attention was focused upon experimental evidence suggesting that the male rat kidney (but not that of the female rat, mouse, or man) contains a unique alpha-2u-globulin protein that can combine with PCB to form hyaline droplets, and also upon a further hypothesis that the hyaline droplet formation in turn can cause cell damage and proliferation and subsequent tumor formation (see section D.1). The implication of this mechanism for some Committee members was that the rat kidney tumor finding may have diminished significance in considerations of tumor risk for humans. Other members, however, took the position that the rat kidney tumor should be considered significant for predicting human responsiveness pending further research relating hyaline droplet formation and tumorigenicity.

- (b) The relevance of the liver tumors in male and female mice was discussed (see section D.2). Committee members who believed that these tumors constituted sufficient evidence of carcinogenicity based their argument upon the facts that both benign and malignant adenomas and carcinomas occurred at a relatively high incidence in male and in female animals, and that rare hepatoblastomas also occurred in the males. Committee members who believed that these tumors constituted limited evidence of carcinogenicity based their arguments upon the facts that the high spontaneous background rate tumor occurred only at the highest dose level in both sexes and only at the end of the study, that no dose-related increase in the proportion of tumors that were malignant was observed, that no decrease in latency was seen, and that negative or inconclusive support for an oncogenic effect was obtained from mutagenicity tests and structure-activity correlations.
- (c) The relevance of extrapolating animal tumor data obtained by the corn oil gavage route of administration to the human situation where the main route of exposure is by inhalation was discussed (see section D.3.). Arguments against making such an extrapolation were that the amounts of PDCB delivered to target organs and the time-course of the deliveries would differ markedly by the two routes, that no proper pharmacokinetic studies have been performed comparing the two routes of administration, and that corn oil per se could have effects on both biochemical and cellular events in the target tissues.

#### G. Classification of Oncogenic Potential

Based upon the above weight of the evidence considerations for PDCB, it follows that the Committee had difficulty in classifying the chemical as to oncogenic potential. The Committee members were divided in their opinion as to whether PDCB should be placed in the B2 or C category. An attempt to reach consensus on this issue by vote resulted in a split opinion, with six members voting for the B2 classification and six voting for the C classification.

This vote was based upon considerations in regard to the water supply as being the main route of exposure of PDCB. However, some panel members felt that if their opinions were to be limited only to the inhalation route of administration, then PDCB would be a Category C oncogen (one

panel member even believed that if only the inhalation route was considered, the scientific data was equivocal and PDCB should thus be placed in Category D oncogen).

Support for placing PDCB in the B2 category was based primarily on the findings that: (1) the chemical produced an increased incidence of malignant tumors, or combined benign and malignant tumors, in multiple species of animals (i.e., renal adenocarcinomas in male rats and hepatocellular adenomas and carcinomas in male and female rats); and (2) the tumors occurred to an unusual degree with regard to high incidence (mouse liver tumors), unusual site of occurrence (male rat renal adenocarcinomas), type of tumor (male mouse hepatoblastoma), and age of onset (male rat renal adenocarcinoma).

Support for placing PDCB in the C category was based upon: (1) the uncertainties associated with the extrapolation of findings from animal studies in which the chemical was administered by gavage in corn oil to the human situation where exposure is primarily by the inhalation route; (2) the concern that the non-neoplastic histopathology present in both the rat and mouse studies might be associated with the neoplastic process and would thus not be seen as a result of the level of exposure of this agent to humans; and (3) an interpretation of the Agency's cancer risk assessment guidelines which would diminish the significance of the finding of tumors in the mouse liver from sufficient to limited (see sections D.2. and F.7.b.) and an interpretation of the rat kidney data as having diminished significance for human risk (see sections D.1. and F.7.a.).

In summary, consideration of the above factors and the criteria contained in EPA Guidelines for Carcinogenic Risk Assessment (CFR September 24, 1986) led the Peer Review Committee to classify PDCB as Category C/Category B<sub>2</sub> carcinogen. This indicates that PDCB is intermediate between a possible human carcinogen (Category C) and a probable human carcinogen (Category B<sub>2</sub>).