------- Dose -------- Administered (ppm)	Human Equivalent (ppm)	--- Tumor Incidence --- Pancreatic acinar adenoma	**Leukemia**	Reference
rats/F344, male. pancreatic acinar adenoma; **leukemia**, all types				
0	0	16/50	11/50	NTP, 1986b
80	80	25/49	20/50	
160	160	30/50	21/50	

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o ADDITIONAL COMMENTS :

The oral slope factors (expressed as per (mg/kg)/day) are based on the tumors of the forestomach in B6C3F1 mice (1.1E-1), tumors of the pancreas in F344 rats (5.8E-1) and **leukemia** in the F344 rat (3.8E-1) individually. A geometric mean of these slope factors was taken as the final estimate [2.9E-1 per (mg/kg)/day] as all three were roughly equivalent and so that relevant data not be discarded.

The unit risk should not be used if the water concentration exceeds 1E+3 ug/L, since above this concentration the slope factor may differ from that stated.

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o DISCUSSION OF CONFIDENCE :

Adequate numbers of animals, lifetime exposure, no effect on survival and adequate dose selection establishing greater confidence in the quantitative estimate.

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both dichlorvos and a major metabolite dichloroacetaldehyde. A structurally related material, dichloropropene, also induces forestomach tumors in rodents. NOTE: The carcinogen assessment for dichlorvos may change in the near future pending the outcome of a further review now being conducted by the CRAVE Work Group.

o ORAL SLOPE FACTOR : 2.9E-1 per (mg/kg)/day
o DRINKING WATER UNIT RISK : 8.3E-6 per ug/L
o DOSE EXTRAPOLATION METHOD : linearized multistage procedure, extra risk
o RISK/WATER CONCENTRATIONS :

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	1E+1 ug/L
E-5 (1 in 100,000)	1E+0 ug/L
E-6 (1 in 1,000,000)	1E-1 ug/L

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o ORAL DOSE-RESPONSE DATA :

Tumor Type -- forestomach, pancreatic, **leukemia** (see table)
Test Animals -- mouse and rat (see table)
Route -- gavage
Reference -- NTP, 1986a,b

---- Dose ----- Administered (ppm)	Human Equivalent (mg/kg/day)	Tumor Incidence	Reference
mouse/B6C3F1, female. forestomach tumors (papilloma, squamous and squamous cell carcinoma)			
0	0.0	5/49	NTP, 1986a
140	15.75	6/49	
280	31.50	19/50	

of 0.1, 1.0, 10, 100, and 500 ppm (measured concentrations of 0.047, 0.46, 4.67, and 234 ppm). This study was flawed by poor survival, tissue autolysis and inadequate number of tissues examined histopathologically. A chronic (2 year) rat (Charles River CD Sprague-Dawley strain) study was conducted by NCI (1977) in which DDVP was fed to groups of 50/sex/dose at 0, 150, and 326 ppm. This study suffered from poor animal survival resulting from intercurrent infection in the animals. A 2-year mouse study was conducted by NCI (1977) wherein DDVP was fed at 0, 318, or 635 ppm. The results were considered equivocal on the basis of insufficient numbers of control animals (dichlorvos controls were pooled with those from other studies). Lastly, in a 2-year inhalation study conducted by Shell Tunstall Laboratories, England (no date), rats were exposed to DDVP at 0, 0.05, 0.5, and 5.0 mg/cu.m. The results were considered equivocal.

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o SUPPORTING DATA :

DDVP was positive in mutation assays using S. typhimurium strain TA1530 and E. coli strains B/r, WP2-hcr, WP2, and Cm 881 (Moriya et al., 1978; Bridges, 1978) without metabolic activation. Results indicative of DNA interactions were obtained in the polA2 assay in E. coli (Rosenkranz, 1973) and for histidine and leucine mutants of Serratia marcescens (Dean, 1972). DDVP was mutagenic in the recessive lethal test using Drosophila (Hanna and Dyer, 1975), and in mouse lymphoma cells in culture without addition of hepatic homogenates (Litton Bionetics, 1985). It was negative in the mouse micronucleus test, in the sister chromatid exchange assay, and in the mouse dominant lethal test (Microbiological Associates, 1985). In addition, dichlorvos alkalates DNA (Segerbaeck and Ehrenberg, 1981).

Dichlorvos is structurally related to dichloropropene (a probable human carcinogen), which causes forestomach squamous cell tumors in rats and mice, lung tumors in mice and neoplastic nodules in the livers of rats.

ORAL EXPOSURE CARCINOGENICITY ASSESSMENT

o CLASSIFICATION	:	B2; probable human carcinogen
o BASIS FOR CLASSIFICATION	:	Significant increases in forestomach tumors in female and male B6C3F1 mice and leukemias and pancreatic acinar adenomas in Fischer 344 rats. Supporting evidence included observation of tumors at other sites in the rat and observation of mutagenicity for

the B6C3F1 strain were treated with dichlorvos at 10 and 20 (mg/kg)/day (males) or 20 and 40 (mg/kg)/day (females), 5 days/week for 104 weeks followed by a 1-week observation period. Corn oil was used as the solvent.

At 40 mg/kg the incidence of squamous papillomas of the forestomach of female mice (18/50) was statistically significantly increased compared with the vehicle control (5/49). There was a significant positive trend in both males and females. The incidence of carcinomas and squamous cell papillomas of the forestomach combined showed a significant trend for the high-dose females (19/50); it was also significantly elevated in a pairwise comparison. It is noteworthy that tumor incidence was elevated at a relatively low treatment dose.

Survival was unaffected by treatment. Based on a significant depression of plasma and RBC cholinesterase in treated mice of both sexes at all doses, dose selection appears to be adequate.

In a 2-year gavage study (NTP, 1986b), rats (60/sex/group) of the F344 strain were treated with 4 or 8 (mg/kg)/day once daily 5 days/week. Survival was unaffected by treatment. Dose selection was adequate based on plasma and RBC cholinesterase suppression.

In the males the incidence of pancreatic acinar adenoma was 16/50, 25/49, and 30/50 at 0, 4, and 8 mg/kg, respectively, which was statistically significantly elevated by pairwise comparison and showed a significant positive dose-related trend. The incidence of alveolar/bronchial adenoma of 3/49 in the high-dose males versus 0/50 in the controls was not significant on a pairwise basis but showed a positive dose-related trend. The incidence of **leukemia** (lymphocytic, monocytic, mononuclear or undifferentiated) was 11/50, 20/50, 21/50 for the males at 0, 4, or 8 (mg/kg)/day, respectively. These values were statistically significantly elevated at 4 and 8 mg/kg/day and also showed a significant dose-related trend. There was a statistically significant increase in lung tumors in the low-dose male rats.

In the females, the incidence (19/50) of mammary fibroadenoma was significant by pairwise comparison and the trend was also significant. When analyzed for all type mammary tumors (fibroma, fibroadenoma, carcinoma, adenocarcinoma or adenoma) the incidence was 11/50, 20/50, 17/50 for 0, 4, or 8 mg/kg, respectively. The mid-dose was significant while the dose-related trend was not. There was a statistically significant increase in mammary tumors in the low-dose female rats.

Four other chronic studies have been conducted on DDVP. A 2-year inhalation study was conducted by Shell Chemical Company (1967) wherein CFE rats (50/sex/dose group) were exposed to DDVP vapors at nominal concentrations

o SPECIES	:	rat
o STUDY TYPE	:	TDLo
o DOSE	:	2060 mg/kg/2Y-C
o EFFECT	:	TUMORIGENIC (Carcinogenic by RTECS criteria)
o EFFECT	:	GASTROINTESTINAL (Tumors)
o EFFECT	:	BLOOD (**Leukemia**)
o REFERENCE	:	Jpn J Cancer Res (Gann), vol 82, pg 157, 1991 (JJCREP)

1 - **IRIS**

NAME OF SUBSTANCE	**Dichlorvos**
CAS REGISTRY NUMBER	62-73-7
SYNONYMS	Dichlorvos

EVIDENCE FOR HUMAN CARCINOGENICITY

o CLASSIFICATION	:	B2; probable human carcinogen
o BASIS FOR CLASSIFICATION	:	Significant increases in forestomach tumors in female and male B6C3F1 mice and leukemias and pancreatic acinar adenomas in Fischer 344 rats. Supporting evidence included observation of tumors at other sites in the rat and observation of mutagenicity for both dichlorvos and a major metabolite dichloroacetaldehyde. A structurally related material, dichloropropene, also induces forestomach tumors in rodents. NOTE: The carcinogen assessment for dichlorvos may change in the near future pending the outcome of a further review now being conducted by the CRAVE Work Group.

o HUMAN CARCINOGENICITY DATA :

None.

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o ANIMAL CARCINOGENICITY DATA :

Sufficient. In a 2-year gavage study (NTP, 1986a), mice (60/sex/group) of

previously caused increased trends for **leukemia** in 2 year studies (pyridine; 2,4,6-trichlorophenol, dichlorvos). The severity of the mononuclear cell **leukemia** in the transplant recipients, as measured by histopathological examination of spleen and liver, was correlated with the changes in tumor growth rates. The in vivo **leukemia** transplant model is a short term assay that could be used to screen a variety of potential chemotherapeutic agents, oir to study structure activity relationships within one class of chemicals. [Dieter MP et al; Leuk Res 13 (9): 841-9 (1989)] **PEER REVIEWED**

NON-HUMAN TOXICITY EXCERPTS

Dichlorvos (dichlorovinyl dimethyl phosphoric acid ester) is a cholinesterase inhibitor used widely as a contact and stomach insecticide for control of internal and external parasites. Carcinogenesis studies were conducted by administering dichlorvos in corn oil by gavage 5 times a week for 103 weeks to groups of 50 male and 50 female Fischer rats at 0, 4, or 8 mg/kg body weight, to groups of 50 male B6C3F1 mice at 0, 10, or 20 mg/kg, and to groups of 50 female B6C3F1 mice at 0, 20, or 40 mg/kg. During the course of the studies, body weights and survival rates of the male and female rats and mice were not different from those of their respective controls; females of both species appeared to gain more weight than controls. Neoplasms induced by dichlorovos included adenomas of the exocrine pancreas (male rats), mononuclear cell **leukemia** (male rats), and squamous cell papilloma of the forestomach (male and female mice; two other female mice had squamous cell carcinomas). Lesions observed in female rats that may have been due to dichlorvos administration included adenomas of the exocrine pancreas and fibroadenomas of the mammary gland. The results demonstrated that dichlorvos is carcinogenic for Fischer rats and B6C3F1 mice. [Chan PC et al; Jpn J Cancer Res 82 (20: 157-64 (1991)] **PEER REVIEWED**

1 - **RTECS**

NAME OF SUBSTANCE	PHOSPHORIC ACID, 2,2-DICHLOROVINYL DIMETHYL ESTER
CAS REGISTRY NUMBER	62-73-7
SYNONYMS	**DICHLORVOS**
CARCINOGENICITY STUDIES	
o ROUTE	: oral

investigate whether exposure to carcinogens in an agricultural setting is related to risk of **leukemia**, a population based control interview study of 578 white men with **leukemia** and 1245 controls living in Iowa and Minnesota /was conducted/. Consistent with recent mortality studies, there were slight, but significant, elevations in risk for all **leukemia** (odds ratio 1.2) and chronic lymphocytic **leukemia** (odds ratio 1.4) for farmers compared to nonfarmers. There were no significant associations with **leukemia** for exposure to specific fungicides, herbicides (including 2,4-D and 2,4,5-T), or crop insecticides. However, significantly elevated risks for **leukemia** of \ 2.0 were seen for exposure to specific animal insecticides including the organophosphates crotoxyphos (odds ratio 11.1), dichlorvos (odds ratio 2.0), and famphur (odds ratio 2.2) and the natural product pyrethrins (odds ratio 3.7) and the chlorinated hydrocarbon methoxychlor (odds ratio 2.2). There were also smaller, but significant, risks associated with exposure to nicotine (odds ratio 1.6) and DDT (odds ratio 1.3). This finding of elevated risks for insecticides used on animals deserves further evaluation. [Brown LM et al; Cancer Res 50 (20): 6585-91 (1990)] **PEER REVIEWED**

NON-HUMAN TOXICITY EXCERPTS

The efficacy of a **leukemia** cell transplant model to measure potential chemotherapeutic activity was tested with five different chemicals that had previously been evaluated in 2 year studies. Leukemic spleen cells from Fischer rats were injected subcutaneously into syngeneic recipients and the effects of chemical treatment on tumor progression were evaluated at 70 days post transplant. The data from the short term assay were in all cases correlated with the trends reported for mononuclear cell **leukemia** in 2 year studies, where two chemicals were reported to decease the incidence and three chemicals were reported to increase the incidence of **leukemia**. Short term treatment with the two chemicals which caused negative trends for **leukemia** (2-ethoxyethanol or ethylene glycol monoethyl ether; 4-hexylresorcinol) delayed and/or reduced tumor growth in the transplant model in a dose related fashion, as exhibited by reduction or elimination of splenomegaly and leukoblastosis, and a reversal in the depression of red blood cell indices or platelet counts. By contrast, the rate of tumor progression was increased in the short term assay of the three chemicals which

SCENARIO - PHYSICIAN REVIEW

A forty-five year old house painter, and former farmworker, who had been complaining to his foreman for two months about generalized weakness, suddenly fainted in the middle of a job. This incident ended his procrastination about seeing his physician, who decided to admit him to the hospital for some tests.

Surprisingly, a routine blood count, combined with his symptoms of long-term weakness, and several unusual skin lesions suggested leukemia. Bone marrow aspiration ultimately confirmed chronic lymphocytic leukemia. Apparently, the patient had only recently turned to painting after 15 years of being an all purpose farm hand in a variety of agricultural settings. Although he generally had no knowledge of what chemicals he worked with over the years, he did remember that dichlorvos was a pesticide he had applied to mushrooms. He had worked at the mushroom farm for a year and protective clothing was not provided.

The physician asked the hospital librarian to run a search in TOXNET, specifically in the HSDB, IRIS, and RTECS files, using the CROSSFILE search capability, to see if there might be an association between dichlorvos and leukemia. Although the search revealed only limited evidence of dichlorvos-induced leukemia in humans, the compound was more clearly implicated as a leukemogenic agent in animals.

The variety of other unknown chemicals the patient had been exposed to over the years made it difficult, however, to confirm dichlorvos as the etiologic agent. Treatment options were discussed with the patient.

[**HSDB,RTECS,IRIS**] SS 1 /cf?
USER:
dichlorvos (name) and all leukemia

Search in progress
SS (1) PSTG (1)

[**HSDB,RTECS,IRIS**] SS 2 /cf?
USER:
prt hits indented cont

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1 - **HSDB**
NAME OF SUBSTANCE **DICHLORVOS**
CAS REGISTRY NUMBER 62-73-7
HUMAN TOXICITY EXCERPTS
Mortality surveys and death certificate studies have suggested an association between **leukemia** and farming. To