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OTS PCB PROGRAM

CANCER HAZARD ASSESSMENT AND RISK ESTIMATES FOR POLYCHLORINATED BIPHENYLS (PCBs)

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Executive Summary

As part of the Environmental Protectio Agency's (EPA's) rulemaking effort under Section 6(e) of the Toxic Substances Control Act (TSCA), the Office of Toxic Substances (OTS) has evaluated the available information on the carcinogenicity of polychlorinated biphenyls (PCBs) (USEPA 1982). As support for the present Uncontrolled PCBs Rule, EPA has developed cancer risk estimates based on anticipated exposure scenarios for the inadvertent generation of PCBs from various industrial processes. This was done in order to determine whether or not inadvertent generation of PCBs might present a significant risk to human health.

The overall conclusions reached by the EPA with regard to the cancer hazard assessment and risk estimates are as follows:

1) Based on an evaluation of the numerous studies in animals, the EPA finds that PCBs have carcinogenic potential.

2) Although individually each of the six cancer studies in animals had certain limitations, the EPA determines that Kimbrough's lifetime study on Aroclor 1260 in female Sherman rats and the National Cancer Institute (NCI) bioassay of Aroclor 1254 in Fischer 344 rats provide adequate data to project cancer risk estimates for humans under specific exposure scenarios.

3) The EPA chose to develop two series of risk estimates. The first series is derived from the incidence of hepatocellular carcinomas found in the Kimbrough et al. study (1975) and the use of the one-hit or linear extrapolation model; the second series is derived from the incidence of total malignancies found in the NCI study (1978) and the use of the multistage

extrapolation model; several risk estimates were also derived from the combined liver tumors found in the NCI study and the use of the multistage extrapolation model.

4) The upper 95 percent confidence limits calculated by using the one-hit linear model and the number of hepatocellular carcinomas from the Kimbrough study are 1.5 times higher than those calculated by using the multistage model and combined number of liver adenomas and carcinomas reported in the NCI study. Furthermore, the 95 percent upper confidence limits calculated for the total malignancies category in the NCI study using the multistage model are approximately three times higher than those calculated for the data in the Kimbrough study. Consequently, the most conservative risk estimates are obtained by using the total malignancies category from the NCI study.

5) Using the most conservative mathematical model, the total malignancies category obtained from the NCI data and the worst-case estimates for exposure, the EPA has determined that there are several exposure scenarios within the seven exposure categories (ambient inhalation, ambient ingestion, occupational inhalation, occupational dermal, consumer inhalation, consumer dermal, consumer ingestion) which project an excess lifetime cancer risk in humans of 1 in 100,000 or greater (1×10^{-5} or greater). However, because the actual exposure to inadvertently generated PCBs are expected to be at levels much less than those used for the worst-case exposure estimates, the projected excess lifetime increase in cancer is estimated to be below the 10^{-5} level in the various scenarios from the above seven exposure categories.

PCBs Introduction

As part of the Environmental Protection Agency's (EPA's) rulemaking effort under Section 6(e) of the Toxic Substances Control Act (TSCA), the Office of Toxic Substances (OTS) initiated efforts to determine whether or not limits could be set on the amounts of PCBs inadvertently produced from various industrial process. To accomplish this, EPA has conducted a health hazard assessment for carcinogenicity, an exposure assessment and a quantitative risk assessment for carcinogenicity, and used the combined results of the above assessments to set such limits on PCBs found in products, water and air.

The purpose of this document is to give the details on the qualitative and quantitative processes involved in the generation of the risk estimates. Following this introduction, the document is divided into five sections. The first section contains the Cancer Hazard Assessment. This is followed by a section containing the experimental data selected for use in the risk estimations and the reasons for their selection. The third section is a short summary of the exposure assessment while the fourth section contains the risk estimates. The final section gives the Agency's overall conclusion about the potential risk to human health from exposure to inadvertently generated PCBs.

Hazard Assessment

Human Studies:

The EPA recognizes that there are substantial deficiencies associated with the available epidemiology studies on PCBs. Because of these weaknesses and limitations, these studies are inconclusive and cannot be used to adequately determine whether or not PCBs are carcinogenic in humans (Discussion and evaluation of these studies can be found in USEPA 1982).

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Animal Studies:

Several studies in animals were of adequate design and duration to assess the carcinogenic potential of PCBs. The Kimbrough et al. (1975) study implicates Aroclor 1260 as a liver carcinogen in Sherman strain female rats while the NCI (1978) study, together with the recent work of Norgen et al. (1981), provides evidence for the carcinogenicity of Aroclor 1254 in Fischer 344 rats. In another much shorter study (Ito et al., 1973; using dd mice, Kanechlor 500 induced well-differentiated hepatocellular carcinomas after only 33 weeks of exposure, thus providing additional evidence for the carcinogenicity of PCBs. A number of studies conducted in rodents for shorter periods of time provide suggestive evidence for the carcinogenicity of several PCB mixtures. These studies demonstrate the induction of hyperplastic or neoplastic nodules, adenofibrosis, or hepatomas--lesions frequently associated with exposure to carcinogens. A workshop sponsored by the National Cancer Institute in 1976, resolved that such neoplastic nodules are "proliferative lesions and are known to be induced by carcinogens and, at the least, they indicate an increased probability for the development of hepatocellular carcinoma" (Squire and Levitt 1975). The absence of induced hepatocellular carcinomas in these studies, therefore, does not constitute a "negative" finding as the duration of testing is inadequate to support such a conclusion (USEPA 1980).

In a long term study by Kimbrough et al. (1975), Sherman strain female rats fed 100 ppm Aroclor 1260 in their diets for 21 months developed well-differentiated hepatocellular carcinomas (26/184) and neoplastic liver nodules (144/184). Only one of 171 control animals developed a carcinoma; no neoplastic nodules were observed. In 183/184 treated and 38/171 control animals, there were also foci or areas of hepatocytes with altered cytoplasm. Classification of lesions was determined according to the guidelines developed at a workshop sponsored by the National Cancer Institute held on December 11-13, 1974 (Squire and Levitt

1978) where some of the slides from the PCB-treated animals were reviewed. This particular work by Kimbrough et al. (1978) followed a series of shorter-term studies by Kimbrough and her co-workers which documented the induction of adenofibrosis in PCB (Aroclor 1260 or 1254)-treated rats (Kimbrough et al. 1972, Kimbrough et al. 1973) and adenofibrosis and/or hepatomas (neoplastic nodules) in PCB (Aroclor 1254)-treated mice (Kimbrough and Linder 1974, Kimbrough et al. 1978). Adenofibrosis (cholangiofibrosis), which was observed in the livers of rats ingesting the PCB for six months, was still present ten months following cessation of treatment. Whether this lesion is persistent could not definitely be determined since high levels of the higher chlorinated biphenyl isomers were still present in adipose tissue and liver. Adenofibrosis usually occurs in rat livers concomitantly with hepatocellular carcinomas and are produced by many known carcinogens (Kimbrough et al. 1978). Whether or not these lesions have the potential to develop into cholangiocarcinomas is still debated.

The National Cancer Institute (1978) dosed 24 Fischer 344 rats of each sex with Aroclor 1254 at one of three doses (25, 50, or 100 ppm) for 104-105 weeks. Matched controls consisted of groups of 24 untreated rats of each sex. Hepatocellular adenomas and carcinomas were found in the dosed groups, but not in the controls (males: mid-dose 1/24, high-dose 3/24; females: mid-dose 1/24, high-dose 2/24). Additionally, a high incidence of "nonneoplastic hyperplastic nodules" was noted in the dosed animals (males: controls 0/24, low-dose 3/24, mid-dose 8/24, high-dose 12/24; females: controls 0/23, low-dose 6/24, mid-dose 9/23, high-dose 17/24). Although the incidences of the tumors were not statistically significant at the $p < 0.05$ level, the occurrence of the hyperplastic nodules was related to administration of the chemical. Adenocarcinomas were observed in the stomach, jejunum, or cecum in two dosed males and in two dosed females. In addition to the adenocarcinomas, a carcinoma was observed in one dosed male. None of these lesions was found

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in control animals. Historical incidences of these tumors at this laboratory (1/400 males (one percent), 2/400 females (0.5 percent)) "suggest that the lesions (although not statistically significant) may be related to the administration of Aroclor 1254." However, the NCI concluded that under the conditions of this bioassay, Aroclor 1254 was not carcinogenic.

Morgan et al. (1981) later reviewed the NCI bioassay whole-tissue specimens of rat stomachs which had been preserved in formalin for six years following completion of the study on Aroclor 1254 discussed above. Since intestinal metaplasia and some adenocarcinomas contain alkaline phosphatase (AP), stomach tissues were stained for activity to pinpoint areas of possible pathological significance for histological examination. "All 191 stomachs available were sectioned through the junction of the pyloric region of the stomach and the duodenum, a known hot spot for gastric neoplasms in humans and rats, as well as at any AP positive sites." Intestinal metaplasia and total lesions in the glandular stomach of the F344 rats increased as a function of Aroclor 1254 concentration in the diet. In some cases, intestinal metaplasia disrupted the muscularis mucosa, had features of adenocarcinoma, and resembled areas of invasive carcinomas. While definite sequence of cancer development from these metaplastic areas could not be demonstrated, intestinal metaplasia "has been strongly associated with the occurrence of stomach cancer in man" (Schottenfeld and Fraumeni, 1982). The initial pathological analysis conducted for NCI (1978) detected one adenocarcinoma of the stomach in an animal from the low dose groups and two in animals from the medium dose groups. One adenocarcinoma of the cecum and one carcinoma of the jejunum were also identified in one and five treated males examined, respectively. Morgan et al. (1981) detected three additional adenocarcinomas of the stomach at sites of AP-positive intestinal

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metaplasia as well as two foci of severe intestinal metaplasia in which adenocarcinoma could not be identified with certainty. Three areas of metaplasia and no adenocarcinomas were identified in the 47 control tissues. The NCI and Morgan et al. results are especially important in light of the fact that the sample sizes used by the NCI were unusually small.

The studies of NCI (1978) and Morgan et al. (1981) were not the first to detect the toxicity of PCBs on the gastrointestinal tract. Gastric lesions, such as epithelial hypertrophy, hyperplasia and ulceration, have been described in PCB-exposed monkeys (Allen and Norback 1973, Allen et al. 1974a, Allen et al. 1974b, Allen et al. 1980) and swine (Hansen et al. 1979). In addition, gastric dysplasia or mucous-filled cysts that penetrate the muscularis mucosa have been observed in PCB-treated rhesus monkeys (Allen and Norback 1973, Becker et al. 1979, Silverman et al. 1979). Allen and Norback (1973) originally commented that such dysplastic lesions were indicative of carcinogenic potential. The results of Morgan et al. (1981) and NCI (1978) are consistent with this idea. These findings are especially significant in light of reports that PCB-exposed humans may also experience prolonged gastric lesions. Several reports indicate that humans have continued to experience gastrointestinal disturbances for years following exposure to PCBs (Urabe 1979, Kuratsune et al. 1976 as cited by Allen and Norback 1977).

Another, much shorter, study by Ito and co-workers (1973) in male dd mice produced well-differentiated hepatocellular carcinomas after only 32 weeks of treatment thus providing unusually strong evidence for the carcinogenicity of PCBs (i.e. Kanechlor 500). In 12 mice fed 500 ppm Kanechlor 500 in their diet for 32 weeks, Ito et al. (1973) observed the induction of nodular hyperplasia in seven animals and well-differentiated hepatocellular carcinomas in five animals. Kanechlor 400 and 300 did not induce either the nodules or carcinoma following the same treatment schedule. Because of the very short periods of

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treatment and the small numbers of animals involved, this is insufficient evidence to show the lack of carcinogenic potential for the Kanechlors 400 and 300. However, the induction of carcinoma by Kanechlor 500 within 32 weeks is an unusually clear indication of such potential.

Later, Ito et al. (1974) found that Kanechlors 500, 400 and 300 also induced nodular hyperplasia and cholangiofibrosis (adenofibrosis), but not hepatocellular carcinomas in rats fed from 500 to 1,000 ppm PCB for 28-52 weeks. In another study, Kimura and Baba (1973) induced multiple adenomatous nodules in the livers of rats fed Kanechlor 400 for 400 days. As with the Ito et al. (1973) study, the duration of these experiments is insufficient to determine the activity of a potential carcinogen. The induction of hyperplastic nodules, however, does suggest that such carcinogenic potential exists.

Two recent abstracts (Weltman and Norbeck 1983a, b) provide additional information regarding the oncogenicity of PCBs in rats. The two abstracts present the preliminary findings of Weltman and Norbeck's work with Aroclor 1260 in rats. Male and female Sprague-Dawley rats were fed PCBs in the diet at 100 ppm for 16 months, 50 ppm for eight months, and a control diet for five additional months. Hepatocellular tumors developed in 99 percent of the 67 surviving females (41 percent mixed hepatocholangiocellular carcinomas, 51 percent hepatocellular cystic cholangiomas, and four percent neoplastic nodules), and in 15 percent of the 46 surviving male rats (11 percent neoplastic nodules, and four percent hepatocellular cystic cholangiomas). In the 81 control rats (32 male and 49 female) examined between the 18th and 29th month of the study, only one "hepatocellular tumor" (undefined), and an incidence of six percent simple cholangioma, two percent cystic cholangioma and four percent cholangiofibrosis were observed. No mixed hepatocholangiocellular carcinomas were observed in the controls.

While these results strongly suggest further evidence for the hepatocarcinogenicity of Aroclor 1260 in rats, few details are presented in the abstracts; further details are needed prior to EPA's final acceptance of this work as an adequate evaluation of oncogenic potential.

The conclusion that PCBs are carcinogenic to rodents was also reached by the International Agency for Research on Cancer. In its Evaluation of the Carcinogenic Risk of Chemicals to Humans (IARC 1978) it is stated that "Kanechlor 500 and Aroclor 1254 are carcinogenic in mice, and Aroclor 1260 is carcinogenic in rats; all induced benign and malignant liver-cell tumors."

Experimental Data for Use in Risk Estimation

EPA agrees that when adequate epidemiology data are not available the best experimental data for risk estimate calculations are obtained from long term studies in animals using two species, both sexes and sufficient numbers of dose levels to obtain dose-response information. As noted above, none of the presently available long term studies on PCBs meet these criteria. However, as will be discussed below, EPA finds that both the Kimbrough et al. (1975) study and the NCI bioassay (1978) when taken together presently provide the most appropriate and adequate data for reasonably estimating quantitative risk.

Kimbrough et al. (1975) is the only long term study which demonstrates a statistically significant increase in a given malignant tumor type induced by PCBs (Aroclor 1260). Although there are several drawbacks to using the Kimbrough study for risk estimation, EPA finds that Kimbrough's experimental design was good in that (1) dosing was for a large proportion of the lifespan of the animals, (2) the food route was appropriate, (3) the dose over time was uniform, (4) there was good documentation of the intake dose, (5) a sufficient number of animals was used

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for statistical tests of increase in tumors, and (6) a thorough description of the pathology was provided. Among the drawbacks, EPA notes that the Kimbrough study used only one dose level (100 ppm), one species (rat), one sex (female) and only one commercial mixture of PCBs (Aroclor 1260).

The total evidence on the carcinogenicity of PCBs does not suggest that the results seen in the Kimbrough study are unique to the female Sherman rat. Although none of the other studies (excluding the NCI study) which tested the carcinogenic activity of PCBs were adequate for risk estimate purposes, the results from these studies clearly demonstrate that other PCB mixtures have carcinogenic potential and that this potential can be expressed in other species, strains and sex. Ito et al. (1973) observed the induction of nodular hyperplasias and well-differentiated hepatocellular carcinomas in 7/12 and 9/12 male ddY mice, respectively, fed 900 ppm Kanechlor 500 in their diet for 12 weeks. Two abstracts by Weltman and Morhack (1983a, b) present preliminary findings that PCBs demonstrate carcinogenic activity in male and female Sprague-Dawley rats fed Aroclor 1260.

Furthermore, the Kimbrough study is the only long-term cancer study which gives a clear statistically significant carcinogenic response even though only one dose level was tested. The use of one dose level does not negate the significance of the biological activity observed; however, the shape of the dose response curve cannot be described from only one data point. Consequently, under these circumstances it is only possible to extrapolate from high doses in animals to lower potential exposure in humans by using the one-hit model for calculating risk estimates. Although EPA recognizes that this model will generate the most conservative risk estimates, its use does enable EPA to make a prudent assessment on the potential risk to humans exposed to levels of PCBs permitted by this rulemaking.

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Among 184 rats treated with 100 ppm PCBs in their diet, Kimbrough et al. (1975) observed statistically significant increases in the incidences of hepatocellular carcinomas and liver neoplastic nodules (treated 144/184; controls 0/173). For the purpose of this risk assessment, EPA has selected to use only the incidence of hepatocellular carcinomas. EPA recognizes neoplastic nodules as part of the toxic manifestations resulting from exposure to PCBs and has included these data in the hazard assessment of PCBs. However, neoplastic nodules have not been included in the risk estimate calculations because they are not of themselves malignant tumors nor can it be determined which nodules will, in fact, develop into tumors. Such nodules are "proliferative lesions and are known to be induced by carcinogens and, at the least, they indicate an increased probability for the development of hepatocellular carcinoma" (Squire and Levitt 1975).

Although the NCI has concluded that under the conditions of the bioassay Aroclor 1254 was not carcinogenic in Fischer 344 rats, (i.e. there were no statistically significant increases in any given tumor type), the EPA has chosen to further evaluate these data since it is the only long term study which provides dose response information. In this evaluation, EPA has looked at: (1) the power of the NCI study to detect statistically significant increases in tumor incidences as limited by the small number of animals used, (i.e. 24 rats/dose/sex); (2) the combining of tumor types; (3) the statistical significance of combined tumor types and; (4) the trends in these combined data.

The major weakness of the NCI study is the small sample size which limits the power of the study to detect statistically significant differences between treated and control groups. Therefore, the EPA has conducted a power test on the NCI data to see how the results in the NCI study compare with the

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statistically significant results from the Kimbrough study. EPA has conducted the power test using the combined incidence of hepatocellular carcinomas and adenomas in the NCI study and the incidence of hepatocellular carcinomas in the Kimbrough study (no hepatocellular adenomas were reported in the Kimbrough study).

The incidence of hepatocellular carcinomas or adenomas observed in the high dose males in the NCI bioassay was 3/34 or 13.5 percent. The incidence of hepatocellular carcinomas or adenomas observed in the high dose females was 3/34 or 8.3 percent. With 34 animals in control and treated group, the power of the study to show an increase of 13.5 percent as statistically significant is about 35 percent. Approximately 100 animals would be needed in each of the control and high dose groups to ensure (with 80 percent probability) that an expected incidence of 13.5 percent would be detected as significant in the study. If the males and females with hepatocellular carcinomas and adenomas are combined, the total incidence is 9/68 (10.4 percent). With 68 animals, the power of the study to show an increase of 10.4 percent as statistically significant is about 40 percent. Neither the incidence of 10.4 percent or 13.5 percent is statistically different ($p > 0.10$) than the incidence of 14.1 percent observed for hepatocellular carcinomas in the Kimbrough study. Thus the two studies are consistent with respect to the incidence of hepatocellular carcinomas or adenomas observed. Clearly, the observation of statistically significant increases in tumor types in the NCI bioassay was precluded by the small sample size used.

As shown in the paragraph above, combining the data from the males and females increases the power of the NCI study from about 30-35 percent to about 40 percent. A review of the NCI report on Aroclor 1254 indicates that there are no qualitative or quantitative differences in response between the treated males and treated females in this study. Therefore, it was deemed appropriate to combine the data from both sexes (i.e., combining

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the rates provides an adequate number of animals per dose group and allows for the best characterization of the dose response).

Since the power of the NCI study can be increased by combining the data from the male and female rats, EPA, therefore, reevaluated the statistical significance of the NCI results using the combined data. Eight categories of tumors were selected for evaluation and these include: leukemias, malignant lymphomas, hematopoietic neoplasms, liver carcinomas, liver carcinomas and adenomas combined, stomach adenocarcinomas, gastrointestinal tract malignancies, and all malignant tumors (combined).

EPA recognizes that NCI only looks for statistically significant increases in specific malignant tumor types when making a judgment on the carcinogenic potential of a chemical. OTS has evaluated the results further than NCI to determine if there is any evidence of carcinogenic activity. Thus, EPA has elected to look at four categories. First, liver carcinomas, stomach adenocarcinomas and gastrointestinal tract malignancies were considered because the NCI study indicated a relationship between treatment and the incidence of these types of tumors. Second, the combined incidence of liver carcinomas and adenomas was addressed because it is the major organ of concern based on results from other studies. Therefore, EPA was interested in detecting any tumorigenic activity in the liver. Third, total malignancies were considered because EPA wanted to estimate the overall carcinogenicity of PCBs in the NCI bioassay. Pooling data across tumor types was considered because there was no evidence of significant differences in increased incidence among the specific sites examined. Also, EPA was trying to determine if PCBs are carcinogenic and not necessary that they are carcinogenic in a specific organ. If restricted to the site-specific evaluation one is forced to assume that PCBs will produce exactly the same types of tumors by the same mechanism in humans as in rats. Fourth, EPA considered leukemias and malignant lymphomas and a combination of these malignancies.

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labelled hematopoietic neoplasms, because 66.1 percent (41/62) of the animals with any malignancy had one of these tumor types.

The detailed tumor data on the eight categories was extracted from the NCI bioassay report (1978) and is presented in Table 1. Note that the categories of stomach adenocarcinomas and gastrointestinal tract malignancies include an additional subcategory for combined sexes ("Morgan et al."). Morgan et al. (1981) reviewed the specimens of the stomachs of the Fisher 344 rats used in the NCI study and found an incidence of adenocarcinoma of the glandular stomach of 0/47, 1/48, 1/48, and 2/48. The "Morgan et al." subcategory under stomach adenocarcinomas includes the tumors in the "original report" combined subcategory. Morgan included, but did not review, the adenocarcinomas of the glandular stomach already noted by NCI scientists. The "Morgan et al." subcategory for gastrointestinal malignancies is a summation of the Morgan et al. and NCI data on glandular stomach adenocarcinomas and the NCI data on other malignancies of the gastrointestinal tract.

Note also that a summation of all the tumor categories in Table 1 beginning with leukemias would not be expected to add to the category of "any malignancy". This is because any animal may have had more than one type of tumor. Thus, "any malignancy" means "at least one type of malignancy."

The statistical significance for each of the eight categories was determined and the p-values appear in parentheses following the tumor incidences in Table 1. P-values were derived using the Fisher Exact Test (Cox 1970). In cases where more than one Fisher Exact Test p-value has been calculated in a given row, a simultaneous comparison using the same control group was made, and the Bonferroni inequality was used to maintain a significance of $p = 0.05$. This has been done for the following reason. When results for a number of treated groups are compared simultaneously with control group results, a correction is

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usually employed to ensure the overall significance level that has been chosen. The Bonferroni inequality requires that for k treated groups, the p-value for each simultaneous comparison must be less than or equal to p-value/k. In the case of Table 1, a p-value or α -level of 0.05 was chosen.

The only dose levels or categories which were statistically significant at $\alpha = 0.05$ were the data for combined sexes at 100 ppm in feed (or 5.00 mg/kg/day) for any malignancy. The p-value for the statistical significance of the 21/48 animals with any malignancy at 5 mg/kg/day, as compared with 9/48 animals in control, was highly significant at 0.0074. The data for female rats at 1.25 mg/kg/day were also significant. This might be a statistical aberration, however, as none of the higher doses was significant.

Two additional tests were conducted on the data at each subcategory (males, females, and combined sexes). The technique used to derive both tests comes from Armitage (1955). The first test is a test for departure from linear trend. If the p-value for departure from linear trend is small (Range ?), then the null hypothesis of linearity (whether the association between dose and response is a linear one) is rejected, and one concludes that dose affects cancer incidence but in a manner more complex than linear. Otherwise, "not significant" (N.S.) is indicated.

The second test determines whether the (linear) slope of the dose-response curve is different from zero at a one-tailed level of significance. If the p-value for slope is small, then the inference is that the slope is significantly different from zero (in a positive direction), indicating a tendency for increasing values of dose to be associated with increasing values of response. Not significant (N.S.) is indicated if the p-value is greater than 0.05.

The results of the test for departure from linear trend showed that the only data to be rejected at $p < 0.05$ as not being linear in dose-response was the female data for any malignancy. However, small numbers of animals and respondents in some tumor categories make interpretation of this test difficult (See footnote *** to Table 1).

The results of the test to determine whether the slope of the dose-response curve is different from zero showed that the categories of "any malignancy" for males and combined sexes are highly significant for slope at $p = 0.002$ and 0.003, respectively. For the other tumor categories, small numbers of animals responding present a problem of interpretation, though high significance was observed for slope in the data for males with leukemias ($p = 0.014$) and combined sexes with malignant lymphomas ($p = 0.004$) and in combined sexes for hematopoietic neoplasms ($p = 0.$) (See cautionary note in footnote *** of Table 1).

After its evaluation of the biological and statistical aspects of the data from the NCI study, the EPA decided to calculate two series of risk estimates using the NCI data. The first series is based on the tumors incidences of combined liver carcinomas and adenomas; the second series is based on the tumor incidences of any malignancy. The EPA is using the NCI study for several reasons. Available risk extrapolation models do not preclude the use of data where there are not statistically significant increases over control at any (or even all) dose levels, though there may be a substantial impact on p-values and confidence limits. In addition, better discrimination between models can be obtained if there is an ample range of doses over which the response is noted. This is another reason for choosing the NCI 3-dose plus control over Kimbrough's 1-dose plus control study. Measures of goodness-of-fit of the models to the available data are also more meaningful with a larger number of different dose-response data points.

The OTE has chosen to use the incidences of combined liver carcinomas and adenomas because the liver appears to be the primary target organ in animals. Also, the power test showed that the incidence of liver tumors observed in the NCI study was within the range projected from the Kimbrough study.

There are several reasons for using the "any malignancy" category as a basis for risk estimates. First, data in this category are highly significant (statistically) at the high dose level; the test for positive slope is highly significant; and there is no significant departure from a linear trend. These data also have denominators of 48, a larger number than the 24 animals of each sex, so that confidence limits of an extrapolated dose-response curve would be narrow.

A further statistical test was conducted on the dose-response data for any malignancy to determine whether there was a significant difference between the male and female responses across dose levels. The test used was Cochran's method of standardized difference (Cochran, 1954). No statistically significant differences (at an α -level of 0.05) were found. This test was conducted primarily to see if there would be problems in using the combined data for any malignancy as a basis for risk extrapolation. It was determined there would be none from a statistical viewpoint.

Exposure Estimates

As part of the Uncontrolled PCBs Rulemaking effort, EPA has developed a quantitative exposure assessment (USEPA, 1984) to estimate levels of inadvertently generated or recycled PCBs to which humans may be exposed as a result of the manufacture processing, distribution in commerce, use, and disposal of these PCBs. These exposure estimates were needed to develop cancer risk estimates which would enable the Agency to determine whether

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or not certain materials containing PCBs at low concentrations could be excluded from the statutory ban on PCBs without endangering human health. EPA was required to consider a large number of exposed populations and had only limited resources to develop the exposure assessment. For each potentially exposed population, EPA developed a worst-case exposure scenario based on the best readily available information. Exposure levels were estimated for the scenario assuming that PCBs were present in the environment at concentrations of 50 ppm, 25 ppm and 2 ppm.

These estimated exposures were deemed "maximum hypothetical exposures," and all actual exposures for the given scenario are believed to be less than or equal to the maximum hypothetical exposures. Whenever the maximum hypothetical exposure level associated with a PCB concentration of 50 ppm was very low, no further work was done on the scenario. Resources were concentrated on those scenarios where the estimated exposure levels could constitute risk to human health. Assumptions for these scenarios were refined to obtain better and more reasonable worst-case estimates of exposure. Except for the alternate scenario for exposures to PCBs in soaps, which appears in Attachment B of the exposure assessment (USEPA, 1984), all of the exposure estimates are maximum hypothetical exposures. All actual exposures are believed to be less than or equal to the estimated exposures.

Risk Estimates

The Kimbrough et al. study allows only the crudest forms of risk modeling because it has only one nonzero dose level; however, there is no question as to the statistical significance of the increase in hepatocellular carcinomas observed. On the other hand, the NCI study allows much more mathematically sophisticated risk modeling and measures of χ^2 goodness-of-fit of the models to the data. However, the study is difficult to interpret because of the question of statistical significance of

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the various tumor types. Indeed, NCI concluded that its study did not establish carcinogenicity. The reasons supporting the use of an "any malignancy" category are given above.

Table 2 presents maximum likelihood estimates and lower 95 percent confidence limits on virtually safe doses (VSD) for a range of excess risks from $1x10^{-1}$ (1 in 10) to $1x10^{-8}$ (1 in 100,000,000); the data used here are the Kimbrough et al. data for hepatocellular carcinomas. Because Kimbrough tested only one nonzero dose level, only the one-hit or simple linear extrapolation could be used. As linear regression gives nearly the same results as the one-hit models at low doses, only one-hit extrapolation was employed. The computer program used was that for the multistage model (GLOBAL82), which degenerates to a one-hit model when only one positive dose level is available. The confidence limits on these virtually safe doses are tight, roughly within a factor of 1.5 of the point estimates at a risk of $1x10^{-6}$ (1 in 1,000,000).

Table 3 presents a similar range of excess risks of any malignancy over background risks based on the NCI bioassay. These risk estimates are derived using five of the most widely used extrapolation models: the multistage, logit, probit, Weibull, and gamma-multihit. (See Appendix B for a discussion of the assumptions and limitations underlying each of these models). DOSE80I, a computer program, was used for all models except the multistage for which the GLOBAL82 was used. The logit and the probit models, ordinarily, are expected to give similar results because of their similar functional form. Estimates from the one-hit model are similar to those estimates made using the multistage model. Simple linear extrapolation is approximated by the lower confidence limits on virtually safe doses (that is, upper confidence limits on risk) from the multistage model. Two types of background cancer incidences were assumed for incorporation in all models except the multistage. Independent background implies that any ongoing background carcinogenic

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processes are independent of the carcinogenic response induced by the administration of the carcinogenic agent under study. Additive background implies, on the other hand, that cancers induced by administration of the chemical under study add to already on-going carcinogenic processes, as if arising from an effective background dose, acting by the same mechanism and producing similar types of tumors. (The implications of assuming the different types of background are discussed in greater detail in Appendix B.) It is not clear at this time which of these two is the more valid assumption; therefore for the four models available that consider both types of background, both are presented. The multistage model is consistent with both assumptions so, traditionally, one does not speak of it as either additive or independent. χ^2 goodness-of-fit p-values were also calculated to give an idea of the fit of the model to the data.

As can be seen from Table 3, the estimates of virtually safe dose at a risk of 1×10^{-6} (1 in 1,000,000) from the independent background models vary a million-fold from 10^{-2} for the probit to 10^{-8} for the gamma-multihit. The additive background models, including the multistage model, are all in the area of 0.16×10^{-4} to 0.17×10^{-3} mg/kg/day. The χ^2 goodness-of-fit test results show the multistage model to be the model with the best fit to the data ($p > 0.9999$) and the additive gamma-multihit, the worst fit (although it is still quite adequate) at $p = 0.5391$. (The dividing line or point for adequate/inadequate fit is assumed to be either 0.05 or 0.01.)

Tables 4 and 5 present the results of two suggested methods for placing confidence limits on virtually safe doses, by (1) using the variance of log-dose and (2) using the variance of the reciprocal of dose. The confidence limits in Table 4, based on the variance of log-dose are generally much wider than those in Table 5, based on the variance of the reciprocal of dose. Confidence limits from the independent models vary widely, while those from the additive models are within factors of 5 of each

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other and are within factors of 4 to 20 of their maximum likelihood estimates at a risk of $1 in 10^{-6}$.

The confidence limits for the multistage model, calculated by a method unique to that model, are within a factor of 1.8 of its maximum likelihood estimate of virtually safe dose at a risk of $1 in 10^{-6}$. Thus the multistage confidence limits are much more narrow or "tight." (See Figure 1, which shows upper confidence limits on risks, rather than lower confidence limits on dose.)

Dr. Kenny Crump, author of the Crump multistage computer programs used to estimate risks, has recommended using the upper confidence limits on risks calculated from a low-dose linear model such as the multistage for decisionmaking (1/17/83 memorandum from K. S. Crump to the Carcinogen Assessment Group). The reasons for this are the incorporation of low-dose linearity in the upper confidence limit and the relative stability of the upper confidence limits compared to the point estimates. This general position is supported by the FDA Advisory Committee (1971) for established carcinogens, the Cancer Assessment Group at EPA, the Subcommittee on Estimation of Risks of Irreversible Delayed Toxicity to the Department of HEW Committee to Coordinate Toxicology and Related Programs (1979) and many other groups.

Table 6 presents, for a range of excess risks from $1 in 10^{-1}$ to $1 in 10^{-6}$, maximum likelihood estimates for leukemia alone over background based on the NCI bioassay. The leukemia category was chosen because of the high percentage of pathology of this type in the NCI bioassay. The risks predicted by the same range of independent and additive background models are within factors of 2 of similar estimates based on any malignancy. Again, estimates of confidence limits on virtually safe doses based on the variance of log dose (Table 7) vary more widely than estimates based on the variance of the reciprocal of dose (Table 8). The multistage estimates of confidence limits are also narrow. This

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model produces the best fit among the models examined. Overall there is much consistency between the estimates based on "any malignancy" and those based only on the incidence of leukemia alone.

Estimates of VSD's for risk of hepatocellular carcinoma from the Kimbrough study are compared with estimates of VSD's based on any malignancy or leukemia alone from the NCI study. Based on the multistage model, the best fitting model ($p > .9000$), the maximum likelihood estimates from Tables 2 and 3 compare very well. It seems then, that it makes little difference whether the Kimbrough or NCI study is used, to base quantitative estimates of cancer risk to humans from exposure to PCBs. In deciding which study to use for extrapolation, several factors should be considered, such as the particular type of Aroclor, since tumor types varied among tests of PCB (Aroclor 1254 and 1260). Strain of animal (Fischer 344 versus Sherman) is also an important factor to consider in selecting the most appropriate study. The extent to which one expects perfect site concordance would also dictate the choice of study.

For purposes of estimating excess lifetime risk, EPA has used the NCI data for total malignancies and for combined liver tumors and the Kimbrough data for hepatocellular carcinomas. Exposure estimates for various subpopulations were provided by the Exposure Assessment Branch, Exposure Evaluation Division (USEPA 1984). Table 9 presents the excess or additional lifetime risk estimates based on total malignancies in the NCI study and hepatocellular carcinomas in the Kimbrough study. The model used to derive these excess risks was the multistage model and the program was GLOBAL83.

For a risk of 1×10^{-5}, the point estimate of VSD based on the Kimbrough study and multistage model is 0.68×10^{-2} (Table 2) compared to the point estimate of VSD from the NCI study, of 0.33×10^{-2} (Table 3). These estimates are within a factor of 2 of

each other, and certainly less than an order of magnitude. For a risk of 1×10^{-5}, the lower confidence limit or VED based on the Rinbrough study and multistage model is 0.49×10^{-2} (Table 3), compared to similar estimates of 0.18×10^{-2} based on the NCI study (Table 4). These estimates are within a factor of 3 of each other. The point of comparison here is the malignancy category that is significant over background, even though Rinbrough used female rats only and the NCI category of any malignancy includes both sexes (Mantel and Schneiderman, 1961). Similar comparisons made among the last 4 columns of Table 9 show the same concordance on a risk basis.

The risks estimated from any model must be modified to obtain estimated "safe" levels for humans. Risks for humans are derived using a species-to-species conversion, assuming that the response is determined by dose per unit body surface area, and that rats have sensitive equal to those for humans. These assumptions seem approximately true for many biologic effects, but their validity for reproductive effects is unknown. The surface area of an animal is very nearly proportional to the 2/3 power of the organism's weight. Thus, the equivalent human exposure is estimated by

$$\frac{d_{human}\ (mg/day)}{S_{human}} = \frac{d_{animal}\ (mg/day)}{S_{animal}} \qquad \text{(Equation 1)}$$

where (S) designates surface area, and (d) designates dose.

Using (W) to designate weight, we have that

$$\frac{d_{human}\ (mg/day)}{(W_{human}\ (kg))^{2/3}} = \frac{d_{animal}\ (mg/day)}{(W_{animal}\ (kg))^{2/3}} \qquad \text{(Equation 2)}$$

It follows that

$$d_{human}\ (mg/day) = d_{animal}\ (mg/day) \left(\frac{W_{human}\ (kg)}{W_{animal}\ (kg)}\right)^{2/3} \qquad \text{(Equation 3)}$$

Dividing each side of this equation by weight of humans ($W_{human}\ (kg)$) and again by the weight of animals ($W_{animal}\ (kg)$) we have on a per unit weight basis

$$d_{human}\ (mg/kg/day) = d_{animal}\ (mg/kg/day) \left(\frac{W_{animal}\ (kg)}{W_{human}\ (kg)}\right)^{1/3} \qquad \text{(Equation}$$

W is assumed to be 350 g or .35 kg for rats and 70,000 g or 70 kg for humans, so that the species-to-species coversion factors between monkey risks and human risk is 3 x 70/0.35 = 5.85. In short, humans are assumed to be about 6 times as sensitive as rats (Mantel and Schneiderman, 1975).

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The estimated exposure duration in years was used to modify the risk estimates for the proportion of an average human lifespan of 70 years that individuals in a given exposure category might be exposed to PCBs. If the exposure duration were 35.5 years, for example, as with exposure due to load.ng/ unloading a liquid (assuming PCBs are present in the liquid at 15 mg/kg), then the cancer risks were reduced by a factor times 35.5/70 or 0.51 of their original size. (It would be best to base such proportion-of-lifetime calculations on results from a differential exposure study; however none was available, and this simplistic multiplication factor is currently the state-of-the-art in this area.) Both "most likely" or point estimates of excess cancer risk and 95 percent upper confidence limits on excess cancer risk are presented. The upper confidence limits from the multistage model exhibit linearity at low exposures. They also assume additivity. Additivity, as mentioned earlier, assumes that the effect of a carcinogenic agent is to act through the same mechanisms as that operating for background process. The upper confidence limits are not markedly more conservative than the point estimates of risk in the case of the NCI total malignancies category. Many other factors mentioned in the other Agencies' risk assessments (FDA, EPA, OTA) influence the results (see Appendix A). Among these are the dissimilarity between residues in fish and water and Aroclor 1254, the levels of PCBs in human adipose tissue, and the small sample sizes in the NCI study.

The extrapolation distance between the lowest experimental dose in the NCI study (1.25 mg/kg/day), and the highest and lowest exposure levels are on the order of from 6 to 48,000,000,000. This is a very wide range. In general, the greater the distance over which risks are extrapolated, the less confidence can be placed in these risk estimates.

Conclusion

The majority of exposure scenarios within the seven exposure categories indicate that the excess carcinogenic risks to typical members of the groups exposed to inadvertently generated or recycled PCBs are expected to be less than 1 in 100,000 (1×10^{-5}) if the estimated risk is accurate. However, as Table 9 demonstrates, there are some exposure scenarios for which the excess carcinogenic risks to humans do exceed 1×10^{-5}. OTP has determined that in these instances the projected estimates of carcinogenic risk are no doubt higher than would be expected because the data selected, the statistical model chosen and the worst-case exposure scenarios all give the most conservative estimates of risk. Support for this conclusion is demonstrated in the following exposure scenario as an example: Continuous exposure via inhalation at the level of quantitation for PCBs in air (10 ug/m^3). This assumes that an individual is constantly exposed to 10 ug/m^3 of PCBs in air for a lifetime. EPA estimates that maximum exposures and risks associated with inhalation of PCBs will be at least one order of magnitude lower and typically two to three orders of magnitude for workers, and three to six orders of magnitude lower for consumers and the general population. Estimated maximum exposure levels are less than levels associated with continuous exposure to the level of quantitation because either:

1) the maximum possible PCB concentration is less than 10 ug/m^3 under the conditions of the scenario, or

2) the duration and frequency of exposure are much lower.

Therefore, for the purpose of this rulemaking, it appears that exposure of humans to the limits which have been designated for the inadvertently generated or recycled PCBs will not present an unreasonable risk to human health.

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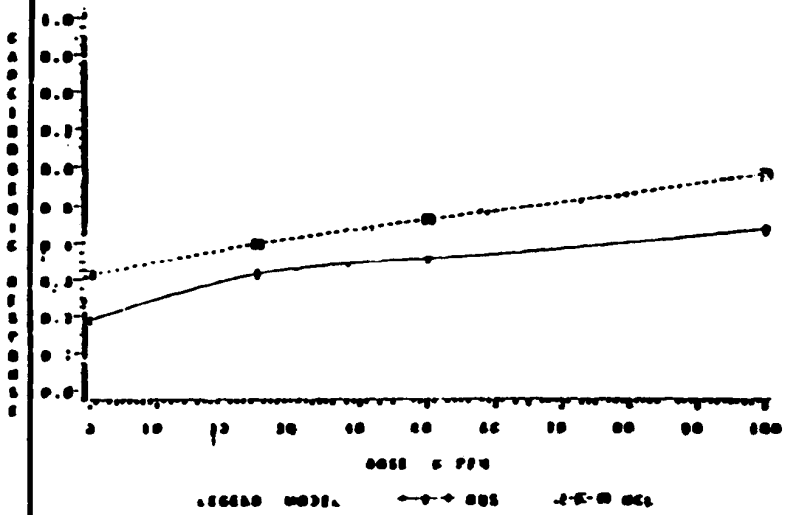
Figure 1

NCI STUDY OF RATS EXPOSED TO PCB



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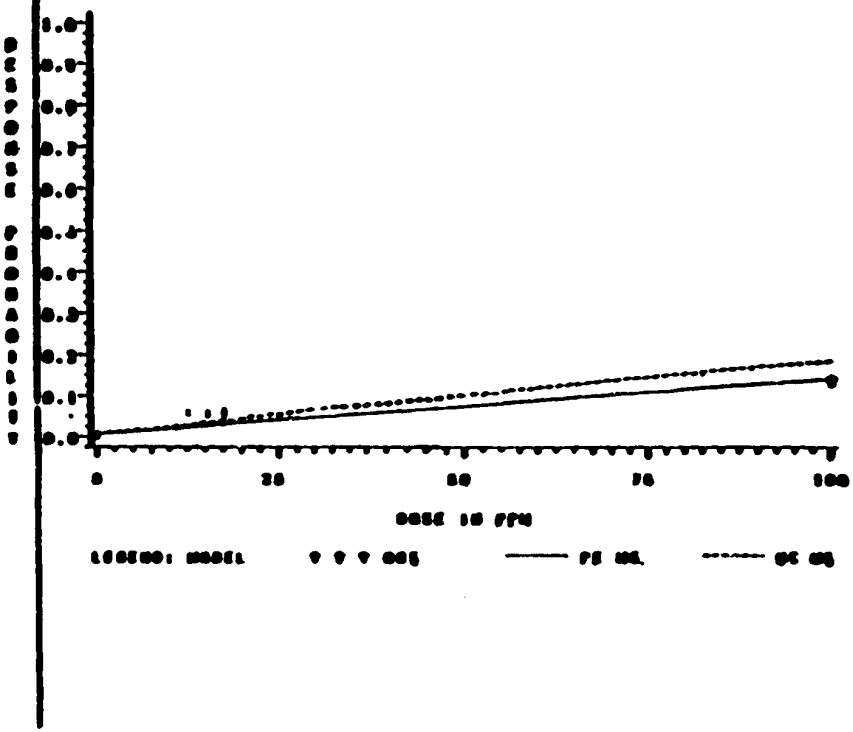
KIMBROUGH HEPATOCELLULAR CARCINOMAS



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TABLES

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Table 1: Actual Data Used for OPS Risk Extrapolation to Humans*

Category	Animals Per Dose Level**					
Dose to Fund	0	25	50	100	Positive Slope	P-Value*** p-value for departure from linear trend
Dose (mg/kg)	0	1.75	2.50	5.00		
Sex Chromosomes						
Males	[illegible]	[illegible] (N.S.)	[illegible] (N.S.)	[illegible] (N.S.)	[illegible]	N.S.
Females	[illegible]	[illegible] ([illegible])	[illegible] (N.S.)	[illegible] (N.S.)	(N.S.)	[illegible]
Combined	[illegible]	[illegible] (N.S.)	[illegible] (N.S.)	[illegible] ([illegible])	[illegible]	N.S.
Hydrocarbons						
Males	[illegible]	[illegible] (N.S.)	[illegible] (N.S.)	[illegible] (N.S.)	[illegible]	N.S.
Females	[illegible]	[illegible] (N.S.)	[illegible] (N.S.)	[illegible] (N.S.)	N.S.	N.S.
Combined	[illegible]	[illegible] (N.S.)	[illegible] (N.S.)	[illegible] (N.S.)	[illegible]	N.S.
Cardiovascular Lesions						
Males	[illegible]	[illegible] (N.S.)	[illegible] (N.S.)	[illegible] (N.S.)	[illegible]	N.S.
Females	[illegible]	[illegible] (N.S.)	[illegible] (N.S.)	[illegible] (N.S.)	[illegible]	N.S.
Combined	[illegible]	[illegible] (N.S.)	[illegible] (N.S.)	[illegible] (N.S.)	[illegible]	N.S.
Hematopoietic System Lesions						
Males	[illegible] (N.S.)	[illegible] (N.S.)	[illegible] (N.S.)	[illegible] (N.S.)	[illegible]	N.S.
Females	[illegible] (N.S.)	[illegible] (N.S.)	[illegible] (N.S.)	[illegible] (N.S.)	N.S.	N.S.
Combined	[illegible] (N.S.)	[illegible] (N.S.)	[illegible] (N.S.)	[illegible] (N.S.)	[illegible]	N.S.
Minor Deviations						
Males	[illegible]	[illegible] (N.S.)	[illegible] (N.S.)	[illegible] (N.S.)	[illegible]	N.S.
Females	[illegible]	[illegible] (N.S.)	[illegible] (N.S.)	[illegible] (N.S.)	N.S.	N.S.
Combined	[illegible]	[illegible] (N.S.)	[illegible] (N.S.)	[illegible] (N.S.)	[illegible]	N.S.
Growth Disturbances						
Males	[illegible]	[illegible] (N.S.)	[illegible] (N.S.)	[illegible] (N.S.)	N.S.	N.S.
Females	[illegible]	[illegible] (N.S.)	[illegible] (N.S.)	[illegible] (N.S.)	N.S.	N.S.
Combined (original report)	[illegible]	[illegible] (N.S.)	[illegible] (N.S.)	[illegible] (N.S.)	N.S.	N.S.
Combined (Morgan et al.)	[illegible]	[illegible] (N.S.)	[illegible] (N.S.)	[illegible] (N.S.)	N.S.	N.S.

Table 1. [illegible]

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

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Table 2

EXCESS RISK TO RATS OF HEPATOCELLULAR CARCINOMA OVER BACKGROUND
(RADIUS IN CENTIMETERS FOR DISPERSION)

Model	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	Maximum Likelihood Estimates of Virtually Safe Doses for Rats Upper							
Multistage (One-Stage)*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	95% One-Sided Lower Confidence Limits on Virtually Safe Doses for Rats Upper							
Multistage (One-Stage)*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

*The multistage model degenerates to the specific case of the one-hit model when only one positive dose found is available.

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Table 3

Excess Risk to Rate of Any Malignancy Over Background
(Based on NCI Accuracy)

Model	1.00E-01	1.00E-02	1.00E-03	1.00E-04	1.00E-05	1.00E-06	1.00E-07	1.00E-08	Goodness of Fit/ Test p-value
	Maximum Likelihood Estimates of Virtually Safe Dose for Data Input								
Multistage	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Independent Probit**	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Independent Logit**	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Independent Weibull**	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Independent Gamma Multistage**	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Additive Probit**	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Additive Logit**	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Additive Weibull**	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Additive Gamma Multistage**	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

*Any p-value greater than 0.50 indicates an adequate fit of the model to the data.

**In many experiments the response of interest also occurs spontaneously in control animals. This background may be assumed to be either independent of the induced response or additive in a mechanistic manner. If the spontaneous and induced responses are assumed to be independent, then the probability of observing a response of either type at dose d is given by: $P^*(d) = q + (1 - q)P(d)$, where $0 < q < 1$ denotes the spontaneous background rate. Under the additivity assumption, the background response may be considered as arising from an effective background dose $v > 0$, with $P^*(d) = P(d + v)$. Although the manner in which background response is accommodated is crucial, the extent to which independence or additivity is indicated by either biological theory or experimental data is somewhat unclear at this time.

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Table 4

95% One Sided Lower Confidence Limits on the Safety Data Shown for Data in Table 11 Based on the Fortran of Log the (Based on GEI PCB Chemistry)

Dose	1.000E-01	1.000E-02	1.000E-03	1.000E-04	1.000E-05	1.000E-06	1.000E-07	1.000E-08
Additive	0.291938E+01	0.268745E+01	0.194795E+00	0.309687E-01	0.106613E-02	0.104572E-03	0.104478E-04	0.104472E-05
Independent Probit	0.228346E+01	0.340488E-02	0.744017E-04	0.168788E-05	0.381870E-07	0.958167E-09	0.[illegible]	0.[illegible]
Independent Logit	0.148834E+01	0.394132E-01	0.999139E-03	0.210478E-04	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]
Independent Weibull	0.965168E+01	0.139887E-01	0.105319E-01	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]
Independent Gamma	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]
Additive Probit	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]
Additive Logit	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]
Additive Weibull	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]
Additive Gamma	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]	0.[illegible]

[illegible] adds background the response of interest also occurs spontaneously in control animals. This background may be assumed to be either independent of the induced response or additive to a quantal-like manner. If the spontaneous and induced responses are assumed to be independent then the probability of observing response of either type at dose d is given by $P^*(d) = q + (1 - q) P(d)$, where $0 < q < 1$ denotes the spontaneous background rate. Under the additivity assumption, the background response may be considered as arising from an effective background dose $z_0 > 0$, with $P^*(d) = P(d + z_0)$. Although the manner in which background response is accommodated is crucial, the extent to which independence or additivity is indicated by either biological theory or experimental data is beyond the scope of this memo.

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Table 5

95.0% One-Sided Lower Confidence Limits on Virtually Safe Doses
for Rats to pay to Table 3 Based on the Variance of the Background of Data
(Based on [illegible])

Model	1.00E-01	1.00E-02	1.00E-03	1.00E-04	1.00E-05	1.00E-06	1.00E-07	1.00E-08
Multistage	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Independent Probit*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Independent Logit*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Independent Weibull*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Independent Gamma Multistage*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Additive Probit*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Additive Logit*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Additive Weibull*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Additive Gamma Multistage*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

*In many experiments the response of interest also occurs spontaneously in control animals. This background may be assumed to be either independent of the induced response or additive to a mechanistic answer. If the spontaneous and induced responses are assumed to be independent, then the probability of observing a response of either type at dose d is given by: $P^*(d) = q + (1 - q)$ [illegible], where $0 < q < 1$ denotes the spontaneous background rate. Under the additivity assumption, the background response may be considered as arising from an effective background dose $e > 0$, with $P^*(d) = P(d + e)$. Although the answer to which background response is accommodated is crucial, the extent to which independence or additivity is indicated by either biological theory or experimental data is somewhat unclear at this time.

Table 8

Bayesian Risk in Units of Incidents Over Background
(Based on NCI PCB Bioassays)

Prior Distribution	Bayesian Unconditional Estimate of Tumorigenic Dose Rate in Rats (rats)								Confidence of 95% Limit (rats)
	1.0E-01	5.0E-02	1.0E-02	1.0E-03	5.0E-04	1.0E-04	1.0E-05	1.0E-06	
1. Uniform	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.95
2. Exponential Model[1]	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.95
3. Exponential Log[2]	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.95
4. Exponential Gamma[3]	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.95
5. Exponential Beta-Gamma[4]	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.95
6. Weibull Model[5]	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.95
7. Weibull Log[6]	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.95
8. Weibull Beta-Gamma[7]	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.95

[1] Any positive number from 0.50 indicates an adequate fit of the model to the data.
[2] The only hypothesis the response of interest (the cancer) spontaneously in control animals. This background may be assumed to be either independent of the induced response or additive to a carcinogenic cancer. If the spontaneous and induced responses are assumed to be independent, then the probability of observing a response of either type at dose d is given by: $P(d) = \alpha + (1 - \alpha) P(d)$, where $0 \leq \alpha \leq 1$ denotes the spontaneous background rate. Under the additivity assumption, the background response may be considered as arising from an effective background dose $\delta > 0$, with $P(0) = P(\delta) = \alpha$. Although the manner in which background response is accumulated is crucial, the extent to which background can alternately be indicated by either biological theory or experimental data is somewhat unclear at this time.

Table 7

95.0% One-Sided Lower Confidence Limits on Virtually Safe Doses
for Rats to pps in Table 6 Based on the Variance
of Log-Dose (Based on [illegible] PCD Discussion)

Model	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Multistage	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Independent Probit*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Independent Logit*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Independent Weibull*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Independent Gamma Weibull*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Additive Probit*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Additive Logit*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Additive Weibull*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Additive Gamma Weibull*	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

*In many experiments the response of interest also occurs spontaneously in control animals. This background may be assumed to be either independent of the induced response or additive in a mechanistic manner. If the spontaneous and induced responses are assumed to be independent, then the probability of observing a response of either type of dose d is given by: $P^*(d) = q + (1 - q)P(d)$, where $0 \le q \le 1$ denotes the spontaneous background rate. Under the additivity assumption, the background response may be considered as arising from an effective background dose $v > 0$, with $P^*(d) = P(d + v)$. Although the manner in which background response is accommodated is crucial, the extent to which independence or additivity is indicated by either biological theory or experimental data is somewhat unclear at this time.

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[illegible]

[illegible] One-Sided Lower Confidence Limits on Virulence Rate Ratios
for Data in Row to Table 6.8 and on the Values of the Background of Some
(Based on NIST PCB Discovery)

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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[illegible] may observe the response of interest also occurs spontaneously in control animals. This background may be viewed to be either independent of the induced response or additive to a undesirable cancer. If the spontaneous and induced responses are assumed to be independent, then the probability of observing a response of either type at dose d is given by $P(d) = q + (1 - q)\,r(d)$, where $0 < q < 1$ denotes the spontaneous background rate. Under the additivity assumption, the background response may be considered as arising from an effective background dose $a > 0$, with $P(d) = r(a + d)$. Although the manner in which background response is accumulated is crucial, the extent to which independence or additivity is indicated by other biological theory or experimental data is beyond [illegible] at this time. .

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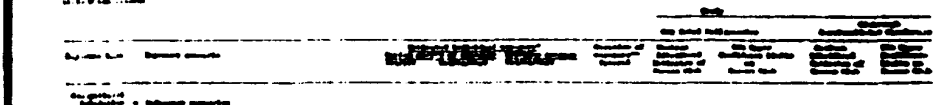

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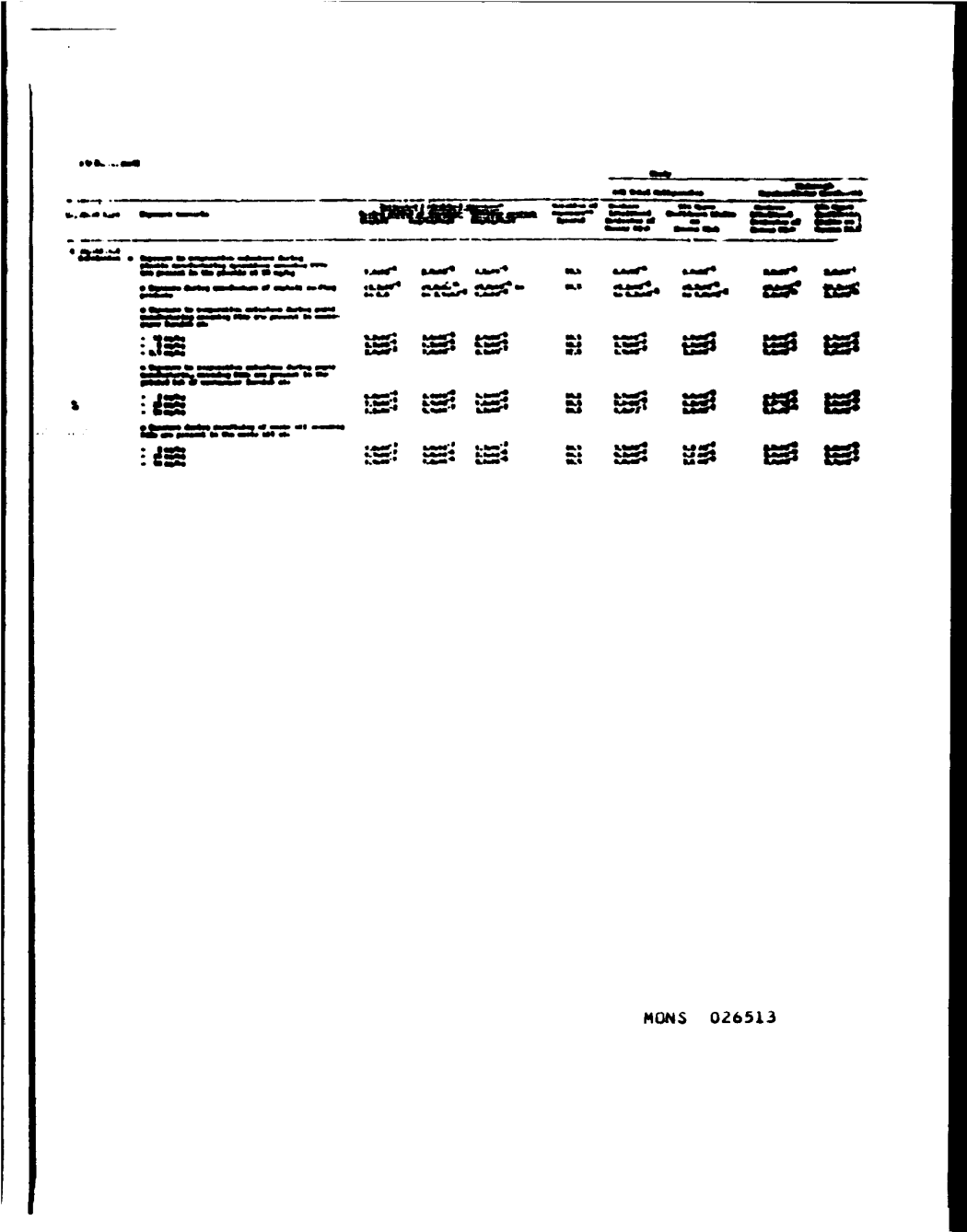

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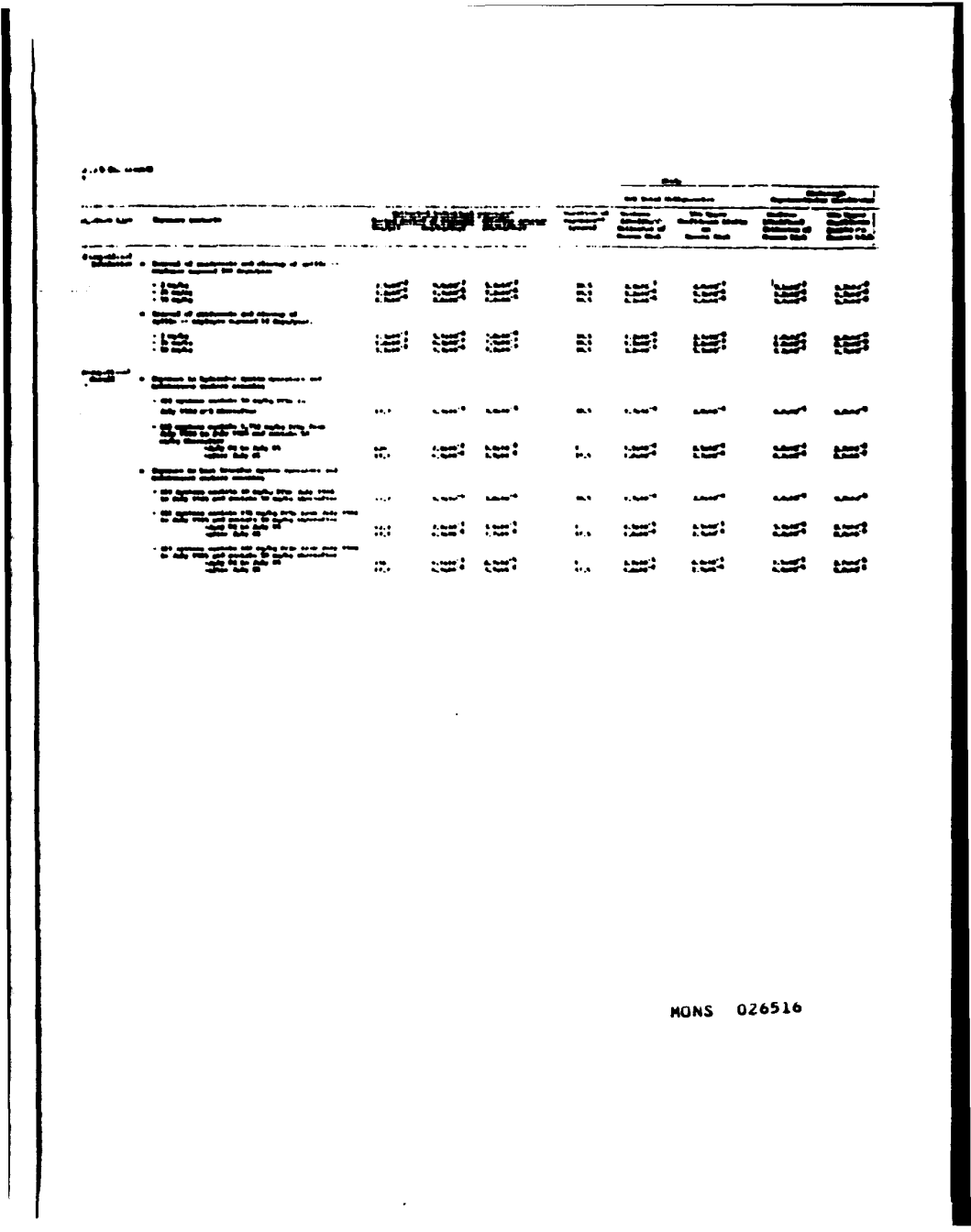

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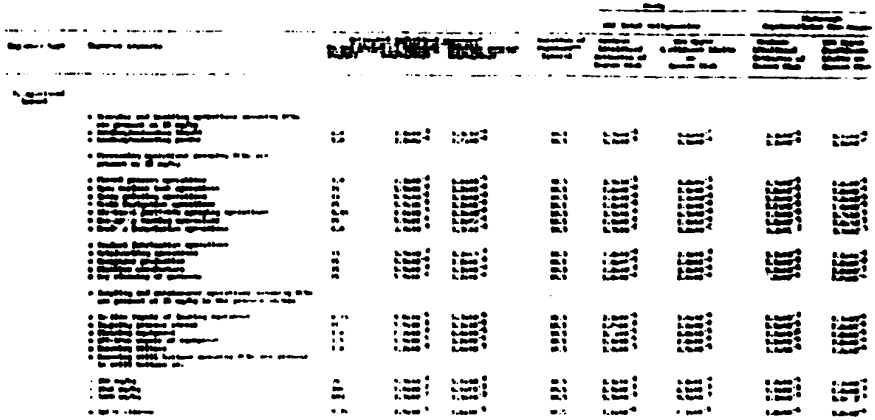

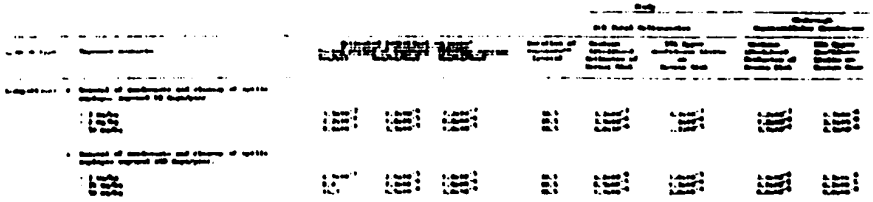

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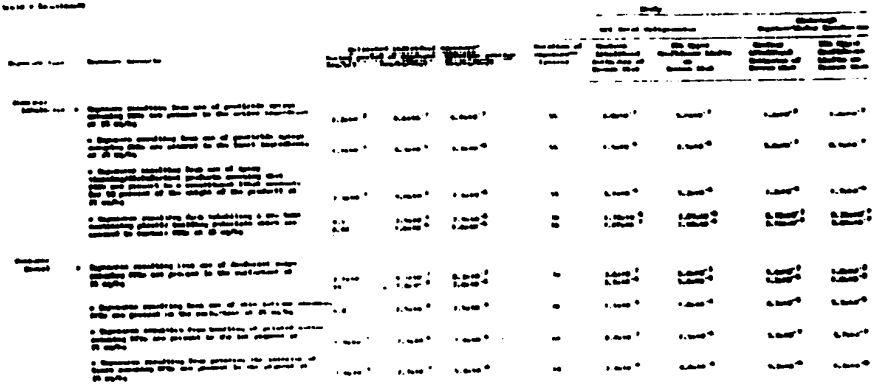

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Appendix A

Previous Quantitative Cancer Risk Assessments on PCBs

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Previous Quantitative Cancer Risk Assessments on PCB's

This appendix consolidates information available from previous quantitative assessments of the carcinogenic risks associated with PCBs. This information was taken into account in the quantitative assessment conducted by OTS. Prior assessments by the EPA Cancer Assessment Group (CAG) (EPA 1980a), the Food and Drug Administration (FDA) (Cordle et al., 1982), and the U.S. Office of Technology Assessment (OTA) (Crump and Masterman, 1979) are reviewed below.

CAG Assessment

A quantitative assessment of the carcinogenic risks of PCBs was submitted by the EPA Carcinogen Assessment Group (CAG) to the Office of Water Regulations and Standards, Criteria and Standards Division (EPA, 1980a).* This risk assessment was used to set an ambient water quality criteria level. Table A-1, reproduced from the CAG report, shows the estimated concentrations of PCBs (or virtually safe doses) corresponding to lifetime cancer risk levels of 10^{-7}, 10^{-6}, and 10^{-5}. These concentrations are, as CAG pointed out, "exceedingly low," and represent additional incidence of cancer in an exposed population. CAG used the "linearized" multistage model (Crump, 1981), which is linear at low doses or exposures so that the additional lifetime risk is directly proportional to PCB intake. CAG's risk assessment considered 1) dietary exposure through consumption of fish and shellfish in which PCBs are known to bioaccumulate, and 2) exposure through drinking water. Exposures from other food sources, air, or occupational exposures were not included in the criteria level derived by CAG.

*The assessment was prepared for CAG by Kenneth S. Crump (conversation with Chai Chen of CAG, November 18, 1982).

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For experimental data, CAG chose the study by Kimbrough et al. (1975) in Sherman rats. CAG considered all of the available mouse studies of PCBs unsuitable for a quantitative risk assessment of cancer because none of them involved feeding for most or all of the animals' lifetime. CAG also criticized the NCI (1978) study in rats, the only other major long-term study of PCB exposure that suggested a carcinogenic effect, as using too few experimental animals to establish a basis for assessing carcinogenic risk.

Although several drawbacks to the Kimbrough study were pointed out in the CAG report, CAG found that Kimbrough's experimental design was good in that (1) dosing was for a large proportion of the lifespan of the animals, (2) the food route was appropriate, and (3) the dose over time was uniform. In addition, CAG noted good documentation of the intake dose, with a sufficient number of animals used for statistical tests of increases in tumors, and a thorough description of the pathology. Among drawbacks, CAG noted that since the Kimbrough study had only one dose level, it could not provide any evidence of the shape of the dose-response curve; moreover Kimbrough et al. tested only one species, one sex (female), and only one commercial mixture of PCBs (Aroclor 1260). CAG also noted that rats appear to be much less sensitive to the acute and subacute effects of PCBs than humans or non-human primates.

Among 184 rats treated with 100 ppm PCB in their diet, Kimbrough et al. observed 28 hepatocellular carcinomas as compared to one hepatocellular carcinoma observed in 171 controls. In the CAG report, the Kimbrough animal data for hepatocellular carcinomas and liver neoplastic nodules--the two tumor types observed by Kimbrough et al.--are combined (this is

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consistent with CAG policy, although it has never been written down); thus at control the proportion responding from the control group was 1/173; at the high dose the proportion responding was 170/184 (CAG 1980a). The average weight of a test rat was assumed to be 400 grams, resulting in a conversion from 100 ppm to 4.42 mg/kg/day. (CAG normally assumes rats weigh 350 grams.)

The formula for calculating virtually safe doses (VSDs) for humans is then

$$VSD = \frac{10 \times 10^{-6}}{q_1^* \times (2 + 0.0065kg \times 46{,}000)}$$

where 2 is a daily consumption of 2 liters of drinking water, 6.5g is an assumed daily consumption of fish and shellfish, 46,000 is the bioconcentration factor (because of the size of this factor, all risk comes from consumption of fish and shellfish, not water), 10^{-6} is the presumed acceptable lifetime risk, and 70kg is the weight of a human.[3]

Based on this formula, HERD has reconstructed the following calculations, with q_1^* as the carcinogenic potency calculated from Crump's model using 1/173 at 0 mg/kg/day and 170/184 at 4.42 mg/kg/day.[4] Thus, q_1^* for rats = .69, and q_1^* for humans would be derived by multiplying by a species conversion of 5.85. This gives 4.01. Thus, VSD = 5.8×10^{-7} mg/l or 0.58ng/l. This is close to .70ng/l, the value derived by CAG for 10^{-5} risk in Table A-1. We are unable to explain the small difference between CAG's calculations of risk and the results of our reconstruction; perhaps Crump made an adjustment for the number of days in the experiment (730) versus the number of days the animals were exposed (645).

[3]The above formula is given in EPA 1980b, p. 79353.

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The CAG report noted that an "acceptable no carcinogenic level" could be established with greater certainty if better quantitative data on carcinogenicity had been available. The report also indicated that studies with larger numbers of animals designed to measure relatively small effects were needed.

FDA Assessment

The second risk assessment under review was conducted by the PCB Risk Assessment Work Force of the Food and Drug Administration (Cordle et al., 1982). Unlike CAG, which preferred the Kimbrough et al. (1975) study, the FDA group used both the Kimbrough (1975) data and the NCI (1978) data to estimate carcinogenic risk to humans from consumption of PCB-contaminated fish. FDA used linear extrapolation from high doses in the animal studies to the lower exposures of consumers of PCB-contaminated fish and water. Linear extrapolation was defended on the grounds that (1) one cannot deduce or directly observe the shape of the low end of the dose-response curve with precision, and (2) among the available methods, linear extrapolation from high to low doses appears to be consistent with what is known about the biological mechanisms of carcinogenesis, and is least likely to underestimate cancer risk. FDA also pointed out that linear extrapolation as used by Crump is the limiting case (upper confidence limit on risk) on his multistage model at low doses; hence the term "linearized" multistage model (Crump, 1981). Instead of strictly following Crump's model, however, Cordle and co-workers placed 99 percent upper confidence bounds on the animal response data to control for the effect of sample size, so that comparisons could be made between experiments. Use of upper bounds on risk together with linear extrapolation provided an additional degree of conservatism in the FDA risk assessment.

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The FDA assessment brought out an additional element of uncertainty, not considered in the CAG assessment, in that toxicity data are not available on the particular set of PCBs that occurs as residues in fish. Due to environmental transformation, the chemical composition of PCB residues in fish differs from that of industrial PCB products (e.g., Aroclor 1254 and 1260), although a typical PCB residue in fish more closely resembles the Aroclor 1254 mixture than the other Aroclors. As FDA pointed out, this raises uncertainties whether the available toxicity data from the Kimbrough et al. (1975) (Aroclor 1260) and the NCI (1978) (Aroclor 1254) studies represented the toxicity of the PCB mixture actually ingested by humans who consume fish.

In view of these uncertainties, FDA computes upper confidence limits on risk, based on the NCI Fischer 344 rat data, for both sexes combined, on total malignancies and liver carcinomas plus adenomas. These data are given in Table A-2.

The dosage levels in Table A-2 are expressed in both ppm and mg/kg/day. The conversion of exposures in ppm to mg/kg/day is by the following relation:

$$\text{dose (mg/kg/day)} = \frac{\text{dose (ppm)} \times F \text{ (kg/day)}}{W \text{ (kg)}} \qquad \text{(Equation 1)}$$

where F is the weight of the food an animal consumes each day, and W is the weight of the average test animal. For rats, F was estimated as 17.5 grams (0.0175 kg), and W as 350 grams (0.35 kg). In addition, FDA also computed estimated risks from the one-sex Sherman rat data on Aroclor 1260 from the Kimbrough study. Because the relative susceptibilities of humans versus experimental animals to the carcinogenic effects of PCBs are not known, FDA noted that the risk estimates could obviously severely overestimate or underestimate human risks. The FDA risk estimates based respectively on the NCI and Kimbrough data demonstrated remarkable agreement, showing that the two different

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rat strains used reacted similarly to PCB carcinogenic insult. These risks are presented as rates per 100,000 in Table A-3 for various tolerances or "acceptable daily intakes" of PCBs and fiftieth and ninetieth percentiles of fish-eating populations. Because exposures in nanograms per liter (ng/l or parts per billion (ppb) are not directly given, it is difficult to compare the results of this risk assessment with results presented by CAG (discussed above) or OTA (discussed below). (However, an attempt at comparison is made on pages A-11 through A-13.) FDA derived the upper confidence limits (number of new cancers per year) given in Table A-4 by assuming that the carcinogenic risk is evenly distributed over a 70-year period, and by multiplying the size of the fish-eating population at risk by the risk estimates shown in Table A-3. FDA also noted that the upper confidence limits (lifetime risks) given in Table A-3 may underestimate risks to neonates who receive PCBs in mothers' milk, but who also continue to consume food contaminated with PCBs in childhood and throughout their lives.

U.S. Congressional Office of Technology Assessment

The PCB cancer risk assessment released by the U.S. Congressional Office of Technology Assessment (OTA) was prepared primarily by Kenneth Crump (Crump and Masterman, 1979), who was also involved in the CAG assessment discussed above. Crump selected three data sets as bases for his computations of virtually safe doses by extrapolating the results of animal experiments to low dose levels. Two of these data sets (Table A-3) are based on the two endpoints of the Kimbrough et al. (1978) rat study--hepatocellular carcinomas and liver neoplastic nodules; the third set is based on data for liver neoplastic nodules provided by a rat study conducted by Industrial Bio-Test Laboratories (IBT, 1971). Crump's rationale for his selection of data sets was as follows. First, as in the CAG assessment, Crump did not use the NCI (1978) study because it involved relatively

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few animals (only 24 per dose group, whereas the usual NCI bioassay uses 50). The Kimbrough, et al. (1975) study was used because it provided the most convincing evidence of the carcinogenicity of PCBs: the study involved a relatively large number of animals, and the increased incidence of hepatocellular carcinomas in the treated group was highly significant. Reasons for selection of the IBT study are not clear, particularly since some IBT data have been found to be "fraudulent". According to Crump and Masterman (1979), the slides from this study were examined at least twice, with markedly different results. Even so, the rediagnosis of the liver pathology indicated a significant tumorigenic effect. There was also unusually high mortality, and interim sacrifices further reduced the numbers of test animals.

Crump and Masterman then selected several high-to-low dose extrapolation procedures: the probit model (Mantel et al., 1975), the one-stage or one-hit model (Crump et al., 1977), and the multistage model (Crump, 1981). The gamma multihit model (Rai and Van Ryzin, 1978) was also considered but not used: it requires data with at least two positive experimental doses and thus could not be applied to either of the Kimbrough et al. data sets; in addition, the computer algorithm for computing the estimates failed to converge for the third data set (IBT) (three positive dose levels).

Table A-6, reproduced from the OTA assessment, presents the computed maximum likelihood estimates (in ppb) of the lifetime dose required to produce additional risks over background of 10^{-8}, 10^{-6}, and 10^{-5}. (CAG considered risk levels of 10^{-7}, 10^{-6}, and 10^{-5} for its virtually safe doses, as shown in Table 1). Lower 95 percent confidence bounds for each of these virtually safe doses were also computed using the same models. In the case of one experimental dose, the one-hit model and multistage model produced identical results.

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Crump believed that the Kimbrough study provided the most convincing evidence of the carcinogenicity of PCBs, and used these data to calculate risks for estimated PCB exposures. The fact that only one dose level of PCBs was tested in the Kimbrough study meant that the one-hit model was the only model that could be utilised. Crump then converted PCB exposure levels from the FDA Total Diet Study (Johnson and Marsha, 1977) to equivalent exposures in rats. The FDA Total Diet Study exposure levels are derived from a "market basket" of food representing a basic 3-week diet of a 16-to-19 year old male; representative samples were collected in each of several geographic areas. The various foods were prepared in the manner in which they would normally be eaten, and then analyzed for residues of various substances, including PCBs. Crump considered the estimates of dose from this study to be tenuous, however. Exposures to PCBs in Michigan sport fish came from a 2-year (1973-1974) study, made under an FDA contract (Humphrey, 1977), of persons who regularly consumed PCB-contaminated Lake Michigan sport fish and randomly selected persons who did not consume such fish.

Crump then fitted a one-stage model to the animal data to estimate the extra risk of hepatocellular carcinomas at this dose. Crump did not mention allowing for any difference between the composition of PCBs in food to which humans are exposed and the composition of Aroclor 1260 used in the experiment. Nor did CAG or FDA factor into their risk estimates the environmental transformation of Aroclor 1254 and 1260, although FDA noted toxicological uncertainties due to these differences in chemical composition. Crump did comment that PCB levels in human adipose tissue are likely to be much greater than corresponding levels in rats for a given level of dietary exposure, but this also was not allowed for in the risk estimates (Table A-7). Upper confidence bounds on these risks are not listed; however, the authors indicated that they could be obtained by multiplying all corresponding risks by 1.5.

From the estimates in Table A-7, Crump computed that nationwide exposure at the dietary level detected in the 1978 Total Diet Study (3.3 µg /day to 8.7 µg/day) would cause 4.1 to 11.1 extra hepatocellular carcinomas in the U.S. Crump also used the one-hit (or one-stage) model with estimates of PCB levels in Lake Michigan fish, to find an average excess of 0.22 hepatocellular carcinomas among residents of Michigan County exposed to PCBs in Lake Michigan. Crump did not indicate whether hepatocellular carcinomas in rats might translate into cancer at other sites in man. Crump went on to estimate the risk of hepatocellular carcinoma in breast-fed infants and concluded that the risk could be much higher than for the U.S. population in general.

Comparative Overview of Previous Assessments

Comparison of results from the FDA, OTA, and CAG risk assessments is difficult due to: (1) the different units in which risk is expressed and (2) incomplete explanation of some crucial assumptions that may have been made in each risk assessment. (3) possible errors in the footnote to Table A-3 of the FDA assessment (see Table A-3). Table A-8 presents the extra lifetime risks of cancer associated with consumption of PCBs in food calculated by FDA and OTA in their separate risk assessments. CAG's risk assessment is not included because data were presented only in terms of virtually safe dose (Table A-1). Differences in estimated risks are readily apparent, due primarily to the different assumptions made in the amount of PCBs that would be ingested and in the size of the exposed population. FDA's risk assessment applies to the 15 percent of the total U.S. population expected to consume those fish species known to be the most highly contaminated with PCBs. The OTA calculations are based on FDA's Total Diet Study (3.3 and 8.7 µg /day) and on estimates of the PCB intake of people who consumed more than 24 pounds of Lake Michigan sport fish per year.

While both the CAG and OTA assessments used the Kimbrough et al. experimental data, CAG used conversions for exposure concentrations due to bioaccumulation levels in aquatic organisms, which OTA did not. In general, all three risk assessments are poorly documented and justified. It is not always clear whether estimated virtually safe doses or increases in risk apply to animals or humans. None of the three published risk assessments explicitly refers to species-to-species conversions (or any other conversions) applied either to the exposure estimates or to the risks from the model. HERD learned from personal communication that CAG did use species-to-species conversions, however.

FDA used linear extrapolation while OTA (Crump and Masterman) used the one-hit model; however, this difference is not great because the one-hit model is nearly linear at low doses. (See Appendix B--High-to-Low Dose Extrapolation) Another obvious difference is that FDA used primarily the NCI study on Aroclor 1254, while OTA dismissed the NCI study in favor of the Kimbrough study on Aroclor 1260. Not only were the number of dose levels different in these studies, but also the responses and tumor types. Finally, CAG, FDA, and OTA appear to have each used different exposure assumptions about the bioaccumulation or bioconcentration levels in aquatic organisms. It is at least known that CAG used a bio-concentration factor of 46,000, even though they reported it as 33,000 in their write-up.

CAG based its assessments on estimates of virtually safe doses (VSD) for consumption of water and fish contaminated with PCBs. The VSD for a risk of 10^{-6} was estimated to be .79 ng/l. Under the assumed exposure conditions this is equivalent to ingesting 3.3×10^{-6} mg/kg/day PCBs. At this risk level HERD estimated the VSDs for rats to be 6.86×10^{-3} mg/kg/day (the Kimbrough study), 3.35×10^{-3} mg/kg/day (NCI study; any

malignancy, both sexes, multistage models) and 8.23×10^{-3} mg/kg/day (NCI study: leukemia, both sexes, multistage model). Applying the conversion factor of 3.85 results in estimated VSDs for humans of 1.17×10^{-3}, 3.73×10^{-3} and 1.41×10^{-3} units mg/kg/day respectively.

The large difference between the VSD, estimated by HERD and CAG can be accounted for as follows. CAG based its estimated on pooled and neoplastic nodules and hepatocellular carcinomas in the Kimbrough study but HERD used only the data on hepatocellular carcinomas, so HERD's estimate of tumor incidence at the one positive dose used in the Kimbrough study is 6.5 times lower than CAG's. HERD also used the NCI bioassay but its tumor incidence was much lower than the pooled incidence in the Kimbrough study. In addition, CAG used Crump's linearized multistage model but HERD used an ordinary multistage model. Thus, CAG used the 95 percent upper confidence limit of the slope on dose in the multistage model to estimate the VSD while HERD used maximum likelihood estimates of slope for its calculations. The differences between the data and models used in the two assessments produced the much higher risk estimates, hence much lower VSD's for specified doses in the CAG assessment.

FDA estimated lifetime risks of cancer from consumption of fish contaminated with PCBs. These estimates can be compared with HERD's estimates of lifetime risks of consumption of contaminated food. At an exposure of from 1.4×10^{-8} to 9.1×10^{-3} mg/kg/day, HERD estimated an upper 95 percent lifetime risk limit to be 8.1×10^{-9} to 3.7×10^{-3}. FDA gives 99 percent upper confidence limits on risks (Cordle et al. 1982; Table A-4) based on the Kimbrough and NCI studies. Exposures were derived from

different levels of fish consumption (Cordle et al. 1982 Table A-3). Extrapolating the dose-risk curve based on total malignancies in the NCI study to a dose of 3.5×10^{-8} mg/kg/day results in a risk estimate of 2.38×10^{-7} which is slightly higher than NERD's estimate. Risk estimates from the other studies used by FDA would be somewhat lower than 2.38×10^{-7}.

OTA applied several dose-response models to data from two studies. However, most of their attention was focused on applying the one-hit model to Kimbrough's data on hepatocellular carcinomas in order to estimate the risk to humans of this cancer from consumption of PCB contaminated food. Again, these risk estimates can be compared with NERD's estimates for risks from consumption of PCBs in food. The risk estimates and doses listed by OTA (Table A-8) are linearly related. Extrapolating this relationship to a dose of 2.5×10^{-8} mg/kg/day gives a risk estimate of 3.95 per one hundred million which is slightly higher but quite similar to the risk of 1.1×10^{-8} estimated by OTB for this exposure.

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Table A-1: CAG's Table for Water Quality Criteria of PCBs*

PCB Exposure	Lifetime Risk Levels and Water Quality Criteria		
	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 6.5g contaminated fish and shellfish per day**	0.0079 ng/l	0.079 ng/l	0.79 ng/l
Consumption of fish and shellfish only**	0.0079 ng/l	0.079 ng/l	0.79 ng/l

*From CAG report (EPA 1980a), p.c-44.

**Approximately 99% of the PCB exposure results from aquatic organisms, which exhibit an average bioaccumulation potential of 31,200-fold. The remaining 1% of PCB exposure results from drinking water.

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Table A-2: Animal Data Used for Risk Extrapolation to Humans in FDA Assessment*

Animal Studies	Dose of Aroclor 1254 fed			
	ppm 0	25	50	100
	mg/kg/day 0	1.25	2.50	5.00
NCI Bioassay - Fisher Rats				
Total Malignancies				
Males	9/24	2/24	9/24	12/24
Females	4/24	13/24	8/24	9/24
Combined	9/48	15/48	17/48	21/48
Liver Carcinoma & Adenoma				
Males	0/24	0/24	1/24	2/24
Females	0/24	0/24	1/24	2/24
Combined	0/48	0/48	2/48	4/48
Hematopoietic Neoplasms				
Males	3/24	2/24	5/24	9/24
Females	4/24	6/24	6/24	6/24
Combined	7/48	8/48	11/48	15/48

*Reproduced from Table 5 in Cordell et al. (1982).

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Table 6.1. Upper Confidence Limits (95%) on Lifetime Risks* of Cancer in Eaters of Fish Species of Interest in PCB Assessment

Animal Studies on which risks are based	50th Percentile Eaters					90th Percentile Eaters				
	Assuming No Tolerance		Assuming Tolerance < 5 ppm	Assuming Tolerance < 2 ppm	Assuming Tolerance < 1 ppm	Assuming No Tolerance		Assuming Tolerance < 5 ppm	Assuming Tolerance < 2 ppm	Assuming Tolerance < 1 ppm
	USA	Lake** Michigan				USA	Lake** Michigan			
Fishbrough - Rats Liver Carcinoma	1.1	10.4	1.2	0.0	0.5	5.4	41.6	1.1	2.5	4.4
NCI Bioassay - Total Malignancies for Male and Female	4.1	50.4	1.7	2.7	1.6	10.6	139.2	9.0	7.2	4.1
NCI Bioassay - Liver Carcinoma and Adenoma for Male and Female	0.5	12.75	0.9	0.6	0.4	2.5	30.5	1.1	1.1	1.0
NCI Bioassay - Hematopoietic Neoplasms for Male and Female	2.7	10.25	2.0	1.0	1.1	7.0	85.1	6.5	6.1	3.0

* All risks are the increased number of cancers per year for the population at risk (15.2% of U.S. population) considering a 70 year life span

**Risk calculated for Lake Michigan sportsfish eaters who consume an average 1.7 µg /kg/day PCB to 1.9 µg /kg/day at the 90th percentile. Risks in other areas having similar sportsfish consumption and PCB contamination are probably similar

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Table 8-4: Upper Confidence Limits on Number of New Cancers per Year in Eaters of Fish Species of Interest in PCB Assessment*

Animal Studies on which risks** are based	50th Percentile Eaters					95th Percentile Eaters				
	Assuming No Tolerance		Assuming Tolerance = 5 ppm	Assuming Tolerance = 2 ppm	Assuming Tolerance = 1 ppm	Assuming No Tolerance		Assuming Tolerance = 5 ppm	Assuming Tolerance = 2 ppm	Assuming Tolerance = 1 ppm
	USA	Lake*** Michigan				USA	Lake*** Michigan			
Dinkrough - Rats Liver Carcinoma	6.2	10.4	5.0	3.0	2.4	16.3	23.0	14.7	10.0	6.7
NCI Dinsdale - Total Malignancies for Male and Female	19.6	32.0	17.6	12.9	7.6	50.6	73.1	44.4	34.3	21
NCI Dinsdale - Liver Carcinoma and Adenoma for Male and Female	4.1	7.2	4.2	1.9	2.0	12.8	17.1	10.9	8.0	4.7
NCI Dinsdale - Nonstagnatic Neoplasms for Male and Female	12.9	21.6	11.4	6.6	5.3	33.4	40.3	31.0	22.5	13.6

* Reproduced from Table 7 in Cordell et al. (1981).

** All risks are the increased number of cancers per year for the population at risk (25.2% of U.S. population) considering a 70 year life span.

*** Risk calculated for Lake Michigan sportsfish eaters who consume an average 1.7 mg/kg/day PCB at 1.9 mg/kg/day at the 90th percentile (4,000,000 people assumed exposed). Risk may be similar for sportsfish eaters in other areas; but data are not available to make estimate.

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Table A-8: Data sets used by Crump for OTA in calculating virtually safe doses*

Data Set No.--I Kimbrough et al. (1975) rat study with Aroclor 1260--

Dietary level (ppm)	(mg/kg/day)	No. of animals	Hepatocellular carcinomas: No. animals with Hepatocellular carcinomas
0	0	173	1
100	5.0	184	26

Data Set No. II-Kimbrough et al. (1975) rat study with Aroclor 1260--

Dietary level (ppm)	(mg/kg/day)	No. of animals	Liver neoplastic nodules: No. of animals with Neoplastic nodules
0	0	173	0
100	5.0	184	146

Data Set No. III-Industrial Bio-Test rat experiment with Aroclor 1260--

Dietary level (ppm)	(mg/kg/day)	No. of animals	Liver neoplastic nodules: No. of animals with Neoplastic nodules
0	0	33	1
1	0.05	75	0
10	0.5	33	9
100	5.0	27	7

*Reproduced from Table 11 in Crump and Masterman (1979).

Table A-6: Virtually safe doses computed by Crump and Masterman (1979), based on data sets shown in Table 5*.

Data Set	Analytic Method	Maximum Likelihood estimates of dose in ppb corresponding to extra risk of:			Virtually safe doses (lower 95% confidence bounds for dose) in ppb corresponding to:		
		10^{-8}	10^{-6}	10^{-5}	10^{-8}	10^{-6}	10^{-5}
Ia	Probit	---	---	---	1.96	14.2	43.4
Ib	One-Hit and Multistage	.0069	.686	6.86	.0051	.511	5.11
IIa	Probit	---	---	---	.025	.180	.55
IIb	One-Hit and Multistage	.00063	.063	.634	.00055	.0511	.511
IIIa	Probit	---	---	---	.176	1.29	3.97
IIIb	One-Hit	.0046	.465	4.65	.00335	.335	3.35
IIIc	Multistage**	.0046	.465	4.65	.00205	.205	3.05

*Reproduced from Table 12 in Crump and Masterman (1979).

**For the gamma multihit model, the computer algorithm failed to converge for Data Set No. III.

Table A-7. Estimates of lifetime extra risk to humans of hepatocellular carcinoma based on a one-hit model to the Kimbrough et al. (1975) rat study*.

Human PCB Dosage	Risks calculated from converting human dose to animal dose on the basis of ppm in diet	mg/kg/day
3.3 ug/day (1976 Total Diet Study)	1/332,000	1/784,000
8.7 ug/day (1975 Total Diet Study)	1/133,000	1/288,000
127ug/day (Avg. intake of people consuming more than 24 lbs./yr. Lake Michigan fish (Humphrey, 1977)	1/8,000	1/20,000

*Reproduced from Table 13 in Crump and Masterman (1978).

Table A-8. Extra lifetime risks of cancer associated with consumption of PCBs in food [a]

Dose (ug/day)	Extra lifetime risk/100,000	Upper limit of new cancers/year
FDA[b]		
9.2[c]	4.4	21
14.9[c]	7.2	34
20.1[c]	9.8	47
OTA[d]		
3.3[e]	0.13	6
8.7[f]	0.39	11
1279[g]	9	--

[a]Reproduced from OTA (1979). OTA obtained FDA data from an earlier, unpublished version of Cordell et al. (1983).

[b]Based on NCI bioassay and total malignancies for males and females.

[c]Based on highest consumers (90th percentile) of fish species contaminated with PCBs if tolerance established at 1.2 or 5 ppm.

[d]Based on Kimbrough (1975, study and hepatocellular carcinomas.

[e]Based on FDA Total Diet Study (1974).

[f]Based on FDA Total Diet Study (1979).

[g]Based on average intake of people consuming more than 24 lbs/year Lake Michigan fish.

Appendix B

High-to-Low Dose Extrapolation

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CONTENTS

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EXECUTIVE SUMMARY

It is often necessary to rely on data from relatively short term experiments on laboratory animals to predict the effect of toxic agents on humans. In order to obtain observable responses within a reasonable time period, the animals have to be exposed to much higher doses, or concentrations, of the toxic agent than those likely to be experienced by humans. Therefore the experimental results are extrapolated from the high observed doses to low doses by fitting a mathematical model and using the model to predict the low dose response. Six models are discussed. They are the probit, logit, Weibull, one-hit, gamma-multihit and multistage models. They are used to describe quantal, or dichotomous, data, i.e. data on whether or not a response is observed in a given time. It is assumed that the administered dose is the same as the effective dose at the site of action. The models fall into two broad classes: (1) threshold models, (2) non-threshold models. The former are descriptive, whereas the latter are derived from plausible biological mechanisms. All six models are non-threshold models, i.e., there is some probability of observing a response no matter how low the dose (provided it is non-zero). Non-threshold models have been recommended for carcinogens because of the nature of the carcinogenic process.

Spontaneous background response can be incorporated into the models as an independent component, as an additive component, or as a mixture of both. Inclusion of even a small additive

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- The Weibull model is a tolerance distribution model which is suggested by human cancer incidence patterns. It behaves in the same way as the logit model at low doses. Estimates of VSD tend to be lower than those estimated by the probit and logit models.

- The one-hit model is based on a mechanistic argument in which it is assumed that there is a response after a target site has been hit by a single biologically effective unit of dose within a given time period. The model is linear at low doses and gives low estimates of the VSD. It is a special case of the gamma-multihit, multistage and Weibull models.

- The gamma-multihit model is a generalization of the one-hit model. It assumes that k hits, are required to cause a response, instead of just one. The dose response curve may be linear, convex or concave at low doses depending on the value of k, and tends to give estimates of the VSD that are similar to the logit model and higher than the multistage model.

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component makes the dose response curve of all six models linear at low doses.

The models are used to estimate a "virtually safe dose" (VSD) which is the dose corresponding to a predetermined low level of increased risk over the spontaneous background response rate. Statistical estimation procedures produce point and interval estimates of the VSD, or provide conservative lower limits based on linear approximations to the dose response curve at low doses. The linear extrapolation methods rely on the assumption that the dose response curve will be convex or linear at low doses. Estimates obtained from the models differ due to the properties of the models:

- The probit model is a tolerance distribution model in which tolerance is assumed to follow a lognormal distribution. It tends to zero very rapidly at low doses and tends to give higher VSD's than other models.

- The logit model is a tolerance distribution which is similar in shape to the probit model but tends to zero less rapidly, thus giving lower VSD's than the probit model. It may be linear, convex or concave at low doses.

- The multistage model assumes that a cell line goes through k distinct stages before becoming cancerous and that the rate at which it progresses through each stage is linearly related to dose. The dose response curve is either linear or convex at low doses. The "linearised" multistage model approximates the dose response curve by a straight line with slope determined by the linear term of the model.

It is difficult to distinguish between models solely on the basis of experimental data. Therefore fitting and comparing the dose response generated, using several different models, is often recommended.

There are three main types of evidence which may be used to determined whether a substance poses a carcinogenic hazard: (1) epidemiologic data from exposed human populations, (2) experimental evidence derived from long-term bioassays of animals, and (3) supportive or suggestive evidence derived from studies of chemical structure or from other short-term tests. Each type of evidence provides useful information but the three sources do not contribute equally to quantitative risk assessment. Evidence from short-term tests, unless supplemented by other types of data, should be considered merely suggestive.

The results of animal studies, having been extrapolated to low dose, are then extrapolated to man. Differences in the

metabolism of chemicals between species often creates the greatest problem in obtaining meaningful extrapolations. Methods of scaling-up animal doses to equivalent human doses have been based on body weight, concentration in the diet, and body surface area. Additional uncertainty is introduced when the route of exposure differs from one species to another.

High- to low-dose extrapolation involves a series of assumptions, some of which are impossible to verify, and necessarily involves a high degree of uncertainty. Nevertheless it is important to obtain the most realistic estimates possible so that appropriate decisions can be made regarding the risk of exposure to toxic substances.

INTRODUCTION

Human beings are exposed to a large number of toxic agents, some of which are amenable to control by imposing regulations regarding their production, use and disposal. In order to make appropriate decisions regarding the regulation of toxic agents, EPA assesses the risk to human health from exposure. Ideally this assessment would be based on epidemiological or clinical studies of human populations. However epidemiological studies are often unsatisfactory for several reasons. For example, it is difficult to measure individual exposure patterns; it may be impossible to eliminate the effects of confounding factors; and the time between exposure and occurence of an observable effect may be very long (up to several decades).

Consequently it is often necessary to rely on relatively short term test carried out on laboratory animals exposed to the toxic agent at very high levels to which humans would not be expected to experience. The results of such tests are subject to two types of extrapolation:

1. The results obtained for laboratory animals at relatively high exposure levels have to be used to predict the effects of relatively low exposure on those animals.

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2. The predicted effects of low level exposure on laboratory animals are used to predict the effects on human health.

Both steps require a series of assumptions, some of which are difficult or impossible to verify, and the process necessarily involves a high degree of uncertainty. Nevertheless, considerable progress has been made in developing means to reduce or overcome these difficulties.

The first step, often referred to as "high- to low-dose extrapolation," is the subject of Chapters 2 and 3 of this report. Chapter 2 describes the particular type of high- to low-dose extrapolation model that will be considered, namely, those involving quantal responses or dichotomous data, and provides general information on the form of the models and the extrapolation process. In Chapter 3 six high- to low-dose models are presented. They are the probit, logit, Weibull, one-hit, gamma-multihit and multistage models. These are the models used by the Design and Development Branch of the Exposure Evaluation Division of EPA to estimate carcinogenic risk. The development, properties, and use of each model are discussed and compared with the other models. Chapter 4 presents the advantages and limitations of various types of evidence which may be used in determining whether a substance poses a health hazard and Chapter 5 addresses the second step described above, namely, extrapolation of animal data to predict human health effects.

Throughout the report the emphasis will be on carcinogenic risk, although many of the procedures are also applicable to other health effects. A bibliography of pertinent literature prior to 1981 is provided by Krewski and Brown (1981).

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HIGH- TO LOW-DOSE EXTRAPOLATION

QUANTAL RESPONSE

The response of an individual to a particular stimulus can be measured by (1) the magnitude of the effect produced (quantitative response); (2) whether or not a response is produced (quantal response); or (3) the time required to produce a specific effect (time to response) (Brown, 1983). This discussion considers only quantal responses.

A typical experiment consists of several groups of animals. Each group is subjected to a different dose, or concentration d, of the agent under test. The numbers of animals in each group that show a responses within a fixed period of time are recorded. This information provides the basis for fitting dose-response curves and extrapolating to low doses. It is assumed that the applied dose or concentration is the same as the effective dose or concentration at the site of action. Pharmacokinetic models have been developed to relate the applied dose to the effective dose (Brown, 1983; Cornfield, 1977), however these models are beyond the considerations of this document.

MODELS FOR EXPERIMENTAL DATA

The models used to described dose-response curves have been classified into two broad categories:

- Tolerance distribution models
- Stochastic or mechanistic models.

(Brown, 1983; Krewski and Van Ryzin, 1981). These categories are not always distinct and some models may belong to both categories.

Tolerance distribution models are based on the concept that each individual in the population has its own tolerance to the test compound. If a dose does not exceed the tolerance of an individual, then there will be no response by that individual. Whereas, if the dose exceeds the tolerance then a response will be observed. Under this assumption, the probability that individual selected at random will respond at dose d is

$$P(d) = Pr(\text{tolerance} \leq d) = G(d)$$

where G is the cumulative distribution of tolerances in the population. $G(t) = F(\alpha + \beta \log t)$, where $t > 0$, $G(0) = F(-\infty)$, F is any standardised cumulative distribution function, and α, β, and any additional parameters that are needed to characterise F. The probit, logit, and Weibull models fall into this class.

Stochastic or mechanistic models are derived from plausible biological arguments which lead to an expression for

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P(d), the probability of an observed response at dose d. The gamma-multihit model, for example, is derived based on the assumption that a response will be induced after a target site has been 'hit' a fixed number of times, and that the occurence of hits follow a homogeneous Poisson distribution. The multistage model is based on the assumption that a response is observed after a number of different random biological events have occurred, the rate of occurrence of each event is possibly different, and the occurrence of the event is dependent on the dose. Based on the underlying biological interpretations mechanistic models are additive; that is. However, there is little evidence available to determine whether these biological interpretations are appropriate. In practice the mechanistic models are used in much the same way as the threshold distribution models. For example, the gamma-multihit model can only be interpreted as a tolerance distribution model when the parameter representing the number of hits is not a positive integer.

All the models described here are non-threshold models. That is, there is some positive probability of observing a response no matter how low the dose (provided it is not zero). There has been much discussion over the existence of thresholds (Schneiderman et al. 1979). It has been argued that responses to carcinogens are less likely to show a threshold effect than responses to other toxic substances because cancer may be produced by an event in a single cell (Crump et al. 1976). Even if a threshold level did exist this level would

probably very among members of the population at risk (Rall, 1979) and the resulting dose response curves would be indistinguishable from those described by non-threshold models (Cornfield et al, 1978). For these reasons, it appears appropriate to use non-threshold models in assessing the risks from exposure to PCBs (State of California, Health and Welfare Agency, 1983).

The main reason for fitting dose response curves from various models to experimental data is to make it possible to extrapolate to low doses. Therefore, the behavior of the model at low doses is of particular importance. The dose-response curve, depending on the model used, may be convex, linear, or concave at low doses (Figure 1). For otherwise comparable curves, a curve that is convex at low doses will lie below one that is linear, and a curve that is concave will lie above the linear curve. Consequently, if the curve is approximated at low doses by a straight line, the approximation will over-estimate risk if the true response curve is convex and under-estimate risk if the true response curve is concave.

INCORPORATION OF BACKGROUND RESPONSE

In an experiment to determine a dose response curve it is possible that some animals might show a response even though they are not exposed to the agent. This spontaneous response may be the result of many factors including the presence of another response causing agent, the genetic make-up of the strain of the

animal, or a background level of toxic substances which are present in the environment. The method of incorporating the spontaneous background response into the model affects the shape of the dose response curve at low doses and therefore is very important in low dose extrapolation.

The background response is most commonly assumed to be either independent or additive (Hoel, 1980). If it is assumed that the probability of a response due to the test agent is independent of the background response then the overall probability of a response, $P^*(d)$, at applied dose d, is given by Abbott's correction,

$$P^*(d) = \gamma + (1 - \gamma)P(d)$$

where $0 < \gamma < 1$ denotes the spontaneous background rate. Under the assumption of additivity the effective dose is assumed to be $(d + \delta)$ where $\delta > 0$ is the increase in effective dose due to background. This gives

$$P^*(d) = P(d + \delta).$$

The additivity assumption is appropriate whenever the test agent shares a mechanism with at least one of the agents producing the background response (Crump et al, 1976). The differences between the independent and additive assumptions are illustrated in Figure 2. A combination of both independent and additive background can be represented by

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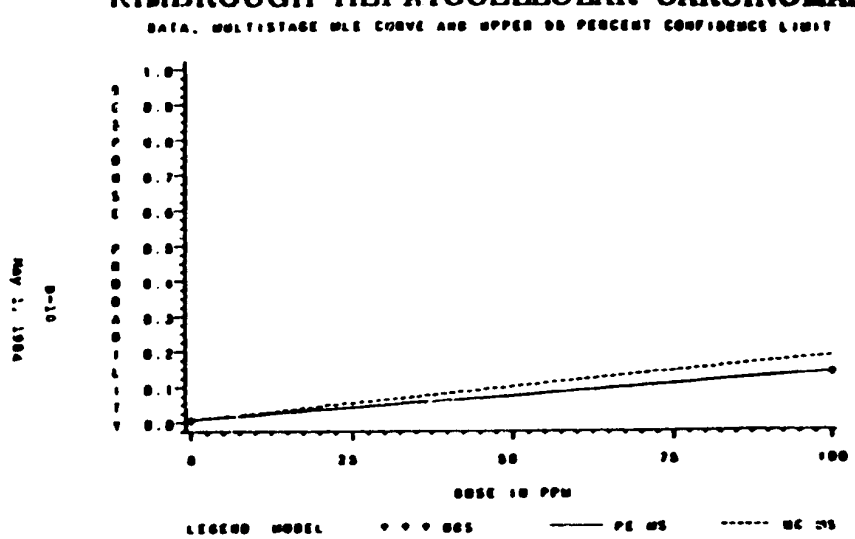

$$P^{*}(d) = \gamma + (1 - \gamma) P(d + \delta).$$

Other effects of background agents such as inhibitory or multiplicative effects are also possible but do not appear in the commonly used models. This is probably because there is no obvious way to include them without additional information.

Discrimination between background additivity and independence on the basis of observed data is often difficult (Brown, 1983) because the shapes of the dose response curves may be almost identical in the observable response range. However the behavior of the two types of models in the low dose range may be quite different.

The excess risk, $\pi(d) = P^{*}(d)$.

For small d, $\pi(d) = d\pi'(0) + O(d^2)$ and therefore $P(d)$ will be almost linear in d whenever $\pi'(0) > 0$ (Crump et al, 1976; Peto, 1978). In the presence of additive background this will be true for all the models discussed here. The same result holds for mixed models which have both independent and additive components. Thus for all models considered in the next chapter the dose response curve will be linear at low doses if there is an additive component of background and may be linear at low doses even if there is not.

Since the low dose risk predicted by a model incorporating an additive background effect tends to be greater than that predicted by a model with an independent background

effect it is often recommended that an additive model be used as a conservative procedure unless there is good evidence for independence (State of California, Health and Welfare Agency, 1983).

EXTRAPOLATION TO LOW DOSE

In risk assessment the primary reason for fitting dose response models to experimental data is to use the model to predict the behavior of the agent at low doses, well below the lowest experimental dose. Since all the models discussed here are strictly increasing with dose (i.e. non-threshold models) the only case in which there may be zero risk of a response is when the dose is zero. This leads to the notion of a 'virtually safe dose' (VSD) which is the dose corresponding to a suitably low level of risk. Most commonly the VSD is defined in terms of an allowable increase over the spontaneous background response rate (Crump et al, 1977). The allowable increase is usually set at between 10^{-4} and 10^{-8} with 10^{-6} being the most common (Cornfield et al, 1973). Other definitions of the VSD are possible but in general the differences between them are small (Krewski and Van Ryzin, 1981).

Maximum likelihood estimation procedures can be used to fit a particular dose response model to a set of experimental data and to obtain point and interval estimates for the excess risk over background, $r(d)$, and the VSD, d^*. Several methods are available depending on the particular model (Krewski and Van

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Rysin, 1981). In this way a VSD is estimated directly from the model.

Other extrapolation techniques have been proposed which, instead of using the fitted curve itself at low doses, use a curve which is likely to lie above the actual dose response curve. The Mantel-Bryan method (Mantel et al, 1975) is one such method which uses the probit model and is described in Probit Model below. Linear extrapolation based on any model (Taylor and Kodell, 1980) or on the multistage model in particular (Crump, 1981) is described in Multistage Model. All these methods rely on the assumption that the extrapolated curve lies above the actual curve and hence provides a conservative estimate of the VSD. ("Conservative" is used here to mean less than or equal to the true VSD.) Linear extrapolation will be conservative when the true response curve is linear or convex but not when it is concave at low doses. Since all the models considered here are linear at low doses when additive background is included and most experimental data appear to be linear or convex at low doses there is reasonable justification for the use of linear extrapolation to provide an upper bound on the risk and consequently a lower bound on the VSD.

MODELS USED IN HIGH- TO LOW-DOSE EXTRAPOLATION

PROBIT MODEL (LOGNORMAL)

The probit model is used to describe dose response curves because (1) the proportion of responders often increases

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monotonically with dose and (3) the response curve is sigmoid when the logarithm of exposure level is used. The probit model is used extensively for interpolation (Finney, 1971) rather than extrapolation to low doses. It is also used to describe distribution, where the probability that an individual selected at random will respond at dose d is given by

$$P(d) = (2\pi)^{-1/2} \int_{-\infty}^{\alpha} \exp(-u^2/2)\, du \qquad (3.1.1)$$

given that $\alpha = a + \beta \log d$, and $\beta > 0$. The probit model has also been used to describe "time to response" data (Peto et al, 1972; Whittemore and Altshuler, 1976).

The dose response curve predicted using this model is S-shaped and symmetric about the 50% response level. With independent background the excess risk over background, $r(d)$ goes to zero very rapidly ($\lim_{d \to 0} r(d)/d^m = 0$ no matter how large the value of m) (Krewski and Van Ryzin, 1981). In the absence of additive background, the probit model cannot accomodate low dose linearity and tends to give higher VSDs than those obtained from other models or from linear extrapolation.

For example, the probit model produced results for hexachlorobenzene which were quite different from the predictions of other models and linear extrapolation. This difference was attributed to the fact that the observed dose response curve for hexachlorobenzene was essentially linear (Krewski and Van Ryzin, 1981). On the other hand, the probit model provides a good description of a response curve for methylcholanthrene (Cornfield

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et al (1978)) and was "reasonably accurate" in predicting the incidence of hepatic angiosarcoma in vinyl chloride workers (Cohring et al, 1978). Standard methods for estimating the parameters of the probit model are available (Finney, 1971).

The Mantel-Bryan procedure (Mantel and Bryan, 1961, Mantel et al, 1975) uses the probit model to obtain a "conservative" estimate of the VSD. The method involves estimating a 99% upper limit, P_0, for the risk at the highest experimental dose, d_0, that yields no response, and then estimating the dose d_1 that corresponds to a specified risk P_1. To do this it is assumed that P(d) is given by 3.1.1, with β arbitrarily set to 1. The justification for this is that observed values from experimental data are generally greater than 1; thus setting $\beta = 1$ is a conservative assumption. However there are problems in using this procedure (Crump, 1977; Salsburg, 1977). The conservativeness of the procedure has also been questioned (Cornfield et al, 1978).

LOGIT MODEL (LOG LOGISTIC)

The logit model is very similar in appearance to the probit model described in the previous section. It is also a tolerance distribution model with the probability of a response given by

$$P(d) = [1 + \exp(-x)]^{-1} \qquad (3.2.1)$$

where $x = \alpha + \beta \log d$ and α and $\beta > 0$ (Ashton, 1972). This model was derived from chemical kinetic theory and was proposed as a dose response model by Worcester and Wilson (1943), and Berkson (1944). Prentice (1976) proposed a more general model which includes both the probit and logit models as special cases.

The dose response curve is S-shaped and symmetric about the 50% response level. Although the logit model is virtually indistinguishable from the probit model in the observable response range, it approaches zero much more slowly than the probit model. With independent background the excess risk, $\nu(d)$, satisfies the limit

$$\lim_{d \to 0} \nu(d)/d^{\gamma} = (1 - r)\theta^{\gamma} > 0$$

(Krewski and Van Ryzin, 1981). Thus at low doses, the $\nu(d)$ dose response curve is linear when $\gamma = 1$, convex when $\gamma > 1$ and concave when $\gamma < 1$. Low dose linearity ($\gamma = 1$) implies a concave dose reponse curve at higher doses. A log-log plot of $\nu(d)$ versus d will be nearly linear at low doses.

Krewski and Van Ryzin (1981) provide general maximum likelihood estimation procedures which are applicable to the logit model. These procedures give point estimates and confidence intervals for $\nu(d)$ and VSDs. In fitting a variety of models to 38 data sets they found that extrapolations based on the logit model were generally close to those extrapolations based on the gamma-multihit model.

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WEIBULL MODEL (EXTREME VALUE)

The Weibull model is a tolerance distribution model which is suggested by human cancer incidence patterns (Cook et al, 1969). The probability of a response at dose d is given by

$$P(d) = 1 - \exp(-\exp(z)) \qquad (1.1.1)$$

where $z = \alpha + \beta \log d$, and α and $\beta > 0$. The model gets its name from the fact that $P(d) = 1 - \exp(-ad^b)$, where $a = \exp(\alpha)$ and $b = \beta$.

A model of this form can be derived as one of two plausible asymptotic distributions that are compatible with quite general assumptions (Pike, 1966). The assumptions are: (1) that cancer begins in a single cell, and (2) that individual cells in a tissue behave independently, and (3) that cancer of the tissue starts when the first cell in the tissue becomes cancerous. The parameter "s" can be interpreted as the time elapsed since the start of application of the dose less a minimum "latent period" during which no tumors will have developed (Peto et al, 1972). When time to the appearance of a tumor can be recorded for each animal, the Weibull model provides a means of taking into account that some individuals might have died from other causes before the presence of cancer could be diagnosed (Peto and Lee, 1973). However when such information is not available the model is used in the same way as any other tolerance distribution model, i.e

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as a description of the distribution of tolerances in the populations.

Scott and Mahn (1980) propose a model based on critical cell clusters which also leads to the Weibull model. Generalised forms of the Weibull model are discussed by Carlborg (1981a) and illustrated by fitting them to the 3-AAF liver neoplasm data of Staffa and Mehlman (1979).

With independent background the excess risk at low doses, $r(d)$, behaves in the same way as the logit model. At low doses, the $r(d)$ dose response curve is linear when $\beta = 1$, convex when $\beta > 1$ and concave when $\beta < 1$. A log-log plot of $r(d)$ versus d will be nearly linear at low doses (Krewski and Van Ryzin, 1981). Low dose linearity (i.e., $\beta = 1$) implies a concave dose response curve at moderate and high doses.

The Weibull model satisfies the regularity conditions necessary to apply the estimation procedures given by Krewski and Van Ryzin (1981).

Peto et al (1972) compared the fit of the Weibull and probit models to data on the effect of cigarette smoke condensate on mouse skin (Day, 1967). They concluded that the Weibull model provided the better fit. The Weibull model also provided a satisfactory fit (based on the usual chi-square statistic) to the 30 data sets examined by Krewski and Van Ryzin (1981). For these data sets, the Weibull model led to estimates of VSDs which were less conservative than the multistage model, but more conservative than the probit, logit and multihit models.

ONE-HIT MODEL (LINEAR MODEL)

The one-hit model is based on a mechanistic argument in which it is assumed that there is a response after a target site has been hit by a single biologically effective unit of dose within a given time period. If the number of hits follows a generalized homogeneous Poisson distribution and γd is the expected number of hits in the time period in the presence of dose d, then the probability of a response is

$$P(d) = \text{Prob (at least 1 hit)} = 1 - \exp(-\gamma d) . \qquad (3.4.1)$$

The same mathematical form of the model can also be derived from the more general assumption that the probability of developing cancer at low doses is directly proportional to dose. Consequently the dose response curve using the single-hit model is, by necessity, linear at low doses and concave at moderate and high doses. Because of its low dose linearity, the one-hit model is often referred to as the linear model. The single-hit model is a special case of the gamma-multihit, multistage and Weibull models.

Estimation procedures given by Krewski and Van Ryzin (1981) apply. However the one-hit model is not identifiable when both independent and additive background effects are included in the model.

The one-hit model does not provide a good fit to many sets of empirical data because the dose response curve is concave

at higher dose levels, whereas many data sets are convex. It appears to be appropriate for only one (hexachlorobenzene) of the 30 data sets considered by Krewski and Van Ryzin (1981). However it has been used extensively in low dose extrapolation as a conservative estimate of risk, assuming that the true dose response curve is likely to be convex at low doses and hence lie below that of the one-hit model (Neel et al, 1971; BEIR Report, 1972; USEPA, 1979). In some situations the one-hit model is only fitted to the lowest dose groups where the experimental data are consistent with the model (Altshuler, 1976).

The model has been criticised as being unduly conservative in some circumstances. (Mantel and Schneiderman, 1975; Guess and Crump, 1977). For example Van Ryzin and Rai (1980) found that for ethylene thiourea the VSD (for risk level 10^{-6}) estimated by the one-hit model was approximately 1/60,000th that of the multihit model and 1/8010th that of the multistage model.

GAMMA MULTIHIT MODEL

The gamma-multihit model is a generalization of the one-hit model and is based on the "hit theory" of carcinogenesis given by Iverson and Arley (1950) or the "particle theory" discussed in Cornfield (1954). It is assumed that k (≥ 1) hits are required to cause a response, instead of only one. Assuming, as before, that the number of hits follows a generalized

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homogeneous Poisson distribution process with mean γd, the probability that an individual will respond at dose d is given by

$$P(d) = 1 - \sum_{j=0}^{k-1} \exp(-\gamma d) \frac{(\gamma d)^j}{j!}$$

$$= \int_0^d [\Gamma(k)]^{-1} \gamma^k t^{k-1} \exp(-\gamma t)\, dt. \quad (3.9.1)$$

(Rai and Van Ryzin, 1979) where $\Gamma(k)$ is the gamma function. This can also be interpreted as a dose response curve generated by a gamma tolerance distribution with scale parameter γ^{-1} and shape parameter k.

The additional parameter, k, allows the gamma-multihit model to exhibit a greater variety of behavior than the one-hit model. Assuming independent background, the excess risk over background, $v(d)$, satisfies

$$\frac{d}{dd} v(d)/dd^k = (1 - \gamma)\, \gamma^k/\Gamma(k+1) > 0.$$

At low doses the excess risk dose response curve is convex when $k > 1$, concave when $k < 1$ and linear when $k = 1$ (one-hit model). The interpretation of negative or non-integer k in terms of the original mechanistic model is unclear. In such cases, it is more appropriate to use a descriptive tolerance distribution approach.

For $k > 1$ the slope $\frac{dv(d)}{dd}$ at $d = 0$ is zero and for $k > 2$, $\frac{d^2 v(d)}{dd^2}$ is also zero (Cornfield et al. 1978). Thus although the dose response curve has no threshold, its behavior at low doses can be very similar to one which does have a threshold.

Estimation methods are given by Rai and Van Ryzin (1979, 1981), and can be carried out with the computer program MULTI80 [Rai and Van Ryzin (1980)].

The gamma-multihit model can fit a wider range of data than either the one-hit or multistage models. It provided a satisfactory fit (chi-square test) to all 20 data sets considered by Krewski and Van Ryzin (1981), whereas the multistage model was satisfactory for 18 of the data sets and the single-hit appeared to be appropriate in only one case. For these data sets the gamma-multihit tended to give estimates of the VSD which were more conservative than the probit model, similar to the logit model and less conservative than the multistage model. The gamma-multihit was also satisfactory in 10 of the 12 sets considered by Rai and Van Ryzin (1979).

Although the gamma-multihit model has been recommended by the Food Safety Council (1978) for use in risk assessment calculations, this recommendation has been criticised by Haseman et al. (1981) for the following reasons:

1. In some cases the gamma-multihit model can "manufacture" a background rate even when there is no evidence in the data to suggest such a rate. This leads to inappropriately high VSDs. This occurred with two of the 14 compounds considered by the Food Safety Council, namely, nitrilotriacetic acid and aflatoxin B$_1$.

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2. When the curve is concave (i.e. k < 1) the model may produce VSD estimates that are unrealistically low. This occurred with vinyl chloride which has a concave dose response curve.

3. It is unclear which method of calculating confidence intervals should be used. Although the formulae for confidence intervals are asymptotically correct they do not appear to be sufficiently good approximations for the finite sample sizes used in carcinogenicity experiments. "Conservative" confidence limits proposed by Van Ryzin and Rai (1980) cannot be used in many cases because of the instability of the estimate of k. Three other methods of calculating confidence intervals have also been suggested (Rai and Van Ryzin, 1981).

The version of the model used by the Food Safety Council incorporates only independent background effects. If even a small amount of additive background effect is included in the gamma-multihit model, the response curve becomes linear at low doses. Hasegawa et al (1981) found when additive background is estimates of the VSD were comparable with those from the multistage model. It appears that when additive background is incorporated some of the problems associated with the gamma-multihit model are less likely to occur.

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MULTISTAGE MODEL

The multistage model was derived to take into account the observation that for many types of cancer, the death rate is proportional to some power of age (e.g. Wordling, 1953). The model was developed by Armitage and Doll (1961) and extended by Crump, et al (1976). The Armitage and Doll model assumes that: (1) a cell line goes through k distinct stages in a specific order before becoming cancerous, (2) the rate at which it progresses through the ith stage is a constant λ_i, (3) different cell lines develop independently, and (4) the time to cancer is determined by the most rapidly developing line. This model predicts that cancer incidence will increase as (age) k^{-1} increases. Pike (1966) argues that the assumptions that individual cells in a tissue behave independently, and cancer occurs when the first cell becomes cancerous, lead to at least two plausible asymptotic distributions for the time of occurrence of cancer, cdf. One of these distributions is the Armitage and Doll model, which is a form of the Weibull model (see Section 3.3). The other distribution is used in a model of Iverson and Arley (1950).

Crump et al (1976) extended the Armitage and Doll model by assuming that λ_i, the rate at which a cell goes through the ith stage, is linearly related to dose, i.e.,

$$\lambda_i = \alpha_i + \beta_i d$$

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where a_i and β_i are non-negative constants. For a fixed time t, the probability of a cancer is approximately

$$P(d) = 1 - \exp\left[-\sum_{i=1}^{k} (a_i + \beta_i d) t^k\right] \qquad (3.6.1)$$

(Crump et al, 1976). Since the exponent in this expression is a polynomial in the dose rate d, the model can be written more generally as

$$P(d) = 1 - \exp\left[-\sum_{i=0}^{k} q_i d^i\right] \qquad (3.6.2)$$

for $q_i \geq 0$ (Guess and Crump, 1976). Expression (3.6.2) is more general than (3.6.1) because although a_i and $\beta_i > 0$ implies $q_i > 0$, the converse is not necessarily true. In the following discussion the term "multistage model" will be used to refer to 3.6.2. This model has been recommended for low-risk assessment of cancer (IRLG, 1978). Further extensions to the multistage model have been made to include situations in which exposure to the carcinogen is not constant, but varies through an individual's lifetime (Whittemore and Keller, 1978; Day and Brown, 1980; Crump and Howe, 1981). Modifications to the multistage model have been made which takes into account an additional induction period before the clinical appearance of cancer (Crump, 1979).

In the case of independent background

$$\lim_{d \to 0} R(d)/d^k = q_k \exp(-q_0) > 0$$

where R (d) is the excess risk of cancer over background and k is the smallest integer (≥1) such that $q_k > 0$(Krewski and Van Ryzin, 1981). Thus at low doses, the dose response curve R(d)is linear if k= 1 (i.e. if the polynomial has a linear term) and convex if k > 1.. The dose response curves derived using the multistage model cannot be concave at low doses, however, it can be simultaneously linear at low doses and convex at moderate doses. When k = 1 the model reduces to the one-hit model.

The multistage model has been criticised on several grounds (Cariborg, 1981b). First it does not describe concave dose response curves such as those observed with DDT, vinyl chloride, diethylstilboestrol and ethylene dibromide. Secondly, the value of k and hence the number of parameters in the model is undefined, although in practice the value of k does not exceed the number of doses used in the experiment (Crump, 1982). Also, the algorithms used for fitting the multistage model tend to lead to the inclusion of the linear term of the polynomial. This produces the highest extrapolated risks and therefore conservative VSDs. Another criticism is that the shape of the curve in the extrapolated low dose region is relatively insensitive to the shape of the dose response function in the observable range. Cariborg proposes a modified form of the Weibull model, which he claims avoids these and other defects of the multistage model.

The constraints on the parameters of the multistage model make estimation more complicated than for other models. However, algorithms are available both for arbitrary k (Guess and Crump, 1977; Howe and Crump, 1982) and fixed k (Hartley and Sielken, 1977). Since the unknown parameters, q_i, must be non-negative, the asymptotic distribution of the vector of the maximum likelihood estimates will generally not be normal (Guess and Crump, 1978). However, if k is known and none of the true q_i are zero, then the asymptotic normal distribution given by Theorem 3 of Krewski and Van Ryzin (1981) applies. If some of the q_i are zero, then simulation studies (Crump, Guess and Deal, 1977) suggest that confidence intervals based on Corollary 1 of Krewski and Van Ryzin will be nearly correct for small k (k = 1 or 2) and will tend to be conservative for larger k. An alternative method of obtaining confidence intervals is used by Hartley and Sielken (1977). They split the data at random into n groups of equal size and calculate confidence intervals for each group. The calculated confidence interval is used to determine the variance of the estimator. The confidence limits obtained in this way will depend on the particular random split used.

When additive background is incorporated into the multistage model, the parameters are subject to additional non-linear constraints which have to be taken into account in fitting the data to the model (Krewski and Van Ryzin, 1981).

Gaylor and Kodell (1980) proposed a linear extrapolation method for obtaining virtually safe doses. The multistage model is first fitted to the observed data and an

upper 97.5% confidence limit is obtained for a dose, d_e, within the experimental range. A straight line joining this point and the origin (see Figure 1) is assumed to lie above the true dose response curve and thus provide a conservative estimate of the VSD. This method was applied to 14 sets of data. In 11 of the 14 sets, provided VSDs which were larger than the lower confidence limit given by Crump et al (1977) for the curve described by the multistage model. This result is apparently due to the very wide confidence limits for the multistage model at low doses (Gaylor and Kodell, 1980).

Gaylor and Kodell's method does not require the use of the multistage model in particular. A valid estimate of an upper confidence limit at a particular dose and the assumption of a convex dose response curve at lower doses are sufficient. If d_A is the VSD corresponding to the multistage or multiple models and d_L is the VSD corresponding to the linear approximation then

$$1 \leq \frac{d_A}{d_L} \leq \frac{p}{k[(1+p)^{1/k} - 1]}$$

$$1 < d_A$$

where p is the excess risk over background (State of California, Health and Welfare Agency, 1982). The linear extrapolation approximates the multistage model quite well for responses which are within 10% of background incidence regardless of the value of k (Crump et al, 1976).

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Crump (1982) proposed another method of linear extrapolation based on the multistage model which has been adopted by the EPA in setting water quality criteria (USEPA, 1980) and in other areas of risk assessment. The method is an improvement of the extrapolation procedure proposed by Crump, et al. (1977) and involves fitting the multistage model to dose response data and calculating the 95% upper confidence limit, q^*, of the parameter q_1. At low doses the excess risk over background is approximately equal to $q_1 \times$ dose. Thus, lower limits on VSDs are calculated using a straight line dose response curve with q^*. This modification on the multistage model has been referred to as the "linearized" multistage model. It has an advantage over the one-hit extrapolation procedure that was used previously, in that all dose groups, not just the lower dose groups, are used.

The computer program, GLOBAL79 (Crump and Watson, 1979), calculates the confidence intervals for the linearized multistage model using the methodology of Crump, 1982. A further improvement is incorporated in GLOBAL82 (Howe and Crump, 1982) so that confidence limits can also be calculated for higher doses where the linear approximation is less likely to be valid. As dose decreases, the difference between the confidence limits calculated by GLOBAL79 or GLOBAL82 also decreases.

DISCRIMINATING AMONG MODELS

Experimental data often provide few clues as to which model to choose since all of the models described above, with the exception perhaps of the one-hit model, might well provide a satisfactory description of the data over the range of experimental doses (Brown, 1981). Unfortunately, although the models may be very similar within the range of observable effects, they can differ considerably in their predictions at low doses (FDA, 1971; Krewski and Van Ryzin, 1981). Of the 19 data sets examined by Krewski and Van Ryzin, 1981 that had convex dose-response curves, the estimated VSDs (for a risk of 10^{-5} or less) had the ordering one-hit < (Weibull, logit, gamma-multihit) < probit. The difference between the one-hit and probit was often several orders of magnitude.

Also, there is really no solid scientific basis for any mathematical model which relates carcinogen exposure to cancer risks at the extremely low levels typical of experimental exposures (USEPA, 1980). Therefore, we must depend on our current understanding of the mechanisms of carcinogenesis for guidance as to which models to use. As indicated in Section 4.1, at present the most widely accepted conceptualization of the carcinogenic process involves the induction (via mutation) of irreversible damage to DNA which results in replication and growth of morphologically altered cells. A very high proportion of agents which cause cancer are mutagenic (Ames, 1979). USEPA (1980) notes that this leads one to expect that the quantal type

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of biological response characteristic of mutagenesis is associated with a linear, non-threshold dose-response relationship. They note that substantial evidence from mutagenesis studies using radiation and a wide variety of chemicals indicates that this type of model is the most appropriate one, particularly at the lower end of the dose-response curve. The linear non-threshold model is also consistent with the relatively few epidemiologic studies of cancer responses to specific agents that contain enough information to make evaluation possible (e.g., radiation-induced leukemia, skin cancer induced by arsenic in drinking water, and liver cancer induced by aflatoxins in the diet). Animal bioassay data also tend to support the linear non-threshold hypothesis (USEPA, 1980). Both IRLG (1979) and USEPA (1980) have supported the use of linear non-threshold models as the primary basis for extrapolation to low levels of the dose-response relationship.

Despite these recommendations, there is still considerable uncertainty involved in determining which model to use. As discussed in Section 2.1, the incorporation of an additive background response into any of the six models discussed in Chapter 3 renders them linear at low doses and all of the models are non-threshold models. An additional point which merits further investigation is the choice of scale on which dose is measured. Three of the six models use log(d) rather than d for reasons which appear historical rather than based on any real biological consideration. The use of "conservative" methods such as taking upper confidence limits on risk and using linear

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extrapolations which lie above the true response curve appear sensible. Conservative assumptions can be taken to an extreme and estimates which have little practical applicability. At present, the best course of action appears to be to consider the predictions of several different methods and make a decision based on a combination of statistical, mathematical and biological judgement (Food Safety Council, 1980).

A recent review of high- to low-dose extrapolation (State of California, Health and Welfare Agency, 1983) came to the following conclusions regarding the use of the six models discussed in this chapter.

- It is not appropriate to apply the concept of "thresholds" to carcinogenesis unless convincing evidence is presented to demonstrate the existence of thresholds for a specific carcinogen in specified circumstances.

- The effect of a carcinogen should generally be assumed to be additive to that of ongoing processes or other agents that give rise to "background" incidence of cancer. Exceptions to this general assumption should only be made where the carcinogen under discussion operates by a mechanism which is distinct from those leading to background incidence.

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- Because of these assumptions, dose-response relationships for most carcinogens are likely to be linear at low doses, and models which incorporate low-dose linearity should be preferred unless there are specific reasons to reject this assumption.

- The current knowledge of the mechanisms of carcinogenic action provides little guidance as to the appropriate choice of dose-response models. Although the assumption of low-dose linearity is most generally accepted for carcinogens that interact directly with DNA (first-stage carcinogens, or "initiators"), dose additivity (with the assumptions discussed previously) will lead to low-dose linearity for carcinogens that act at any stage.

- The multistage model is an appropriate method for dose extrapolation in many cases. The most important circumstances in which the multistage model may be judged inappropriate are when empirical data indicate a dose-response curve of a "quasi-threshold" type--flat for two or three dose levels but then curving sharply upwards. In these circumstances, the multistage model may underestimate the number of stages and overestimate the low-dose risks. For such data, the gamma multi-hit model provides a practical alternative.

- The Mantel-Bryan model has little biological basis and is likely to underestimate risks at low doses; hence, it should not be used for low dose extrapolation.

- For any extrapolation model, both point estimates of risk and upper confidence limits should be calculated and appropriately identified.

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