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# Quantitative cancer assessment for vinyl chloride: indications of early-life sensitivity[1]

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**Abstract**

Complementary sources of information are analyzed to characterize the early-life cancer risk from inhaling vinyl chloride. A study of partial-lifetime exposures suggests that the lifetime cancer risk depends on age at exposure, with higher lifetime risks attributable to exposures at younger ages. Studies of newborn animal exposures further demonstrate that a brief exposure in newborns can, by the end of life, induce a higher incidence of tumors compared to long-term exposure occurring later in life, including tumor types not induced by exposure later in life. An empirical, quantitative approach is used to model early-life sensitivity to inhaled vinyl chloride, supplementing conventional approaches for estimating the increased cancer risk from lifetime exposure. A single estimate is not presumed to apply to the entire population; instead, the new approach makes distinctions about the cancer risks for different population segments. This assessment shows one way such information might be analyzed, presented, and used to assess actual exposure situations.

*Keywords:* Vinyl chloride; Early-life sensitivity; Cancer risk; Exposure; Risk assessment

## 1. Introduction

Cancer risk assessments are generally conducted and applied to a whole population; differential risk assessments for individual subpopulations are usually not available. This stems from a lack of studies providing information about potentially sensitive subpopulations as well as a lack of methods for assessing differential risks. Vinyl chloride, however, is an example where several innovative laboratory studies provide information about a sensitive period occurring early in life. These studies can be analyzed to more fully characterize the potential for increased early-life risks.

Several sources of information can be brought together to characterize the human cancer risk from inhaling vinyl chloride. Epidemiologic stu-

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dies of workers exposed to vinyl chloride show an increased incidence of angiosarcomas; laboratory studies have induced similar tumors following long-term exposure in three animal species. A study of partial-lifetime exposures in these animal species suggests that the lifetime risk of cancer depends on the age at exposure, with higher lifetime risks attributable to exposures at younger ages. Studies of newborn animal exposures further demonstrate that a brief exposure in newborns can, by the end of life, induce a higher incidence of tumors compared to long-term exposure occurring later in life, including tumor types not induced by exposure later in life.

## 2. Studies analyzed

ATSDR (1988) cites several reports demonstrating a causal association between occupational vinyl chloride exposure and various forms of cancer. Most convincing is the association with liver angiosarcoma, a rare form of cancer. Cancer assessments by IARC (1987) and US EPA (1991) found the human evidence sufficient, leading to an overall characterization of vinyl chloride as a known human carcinogen. Studies using laboratory rats, mice, and hamsters confirm the human observations; in particular, liver angiosarcomas were induced in all species. This uncommon demonstration of site concordance makes extrapolation of the animal results to humans especially credible.

In addition to these studies that led to the identification of vinyl chloride as a known human carcinogen, several studies with novel experimental designs provide evidence that early life can be a sensitive period for exposure. Drew et al. (1983) studied the effect of age and duration of vinyl chloride exposure on cancer incidence.

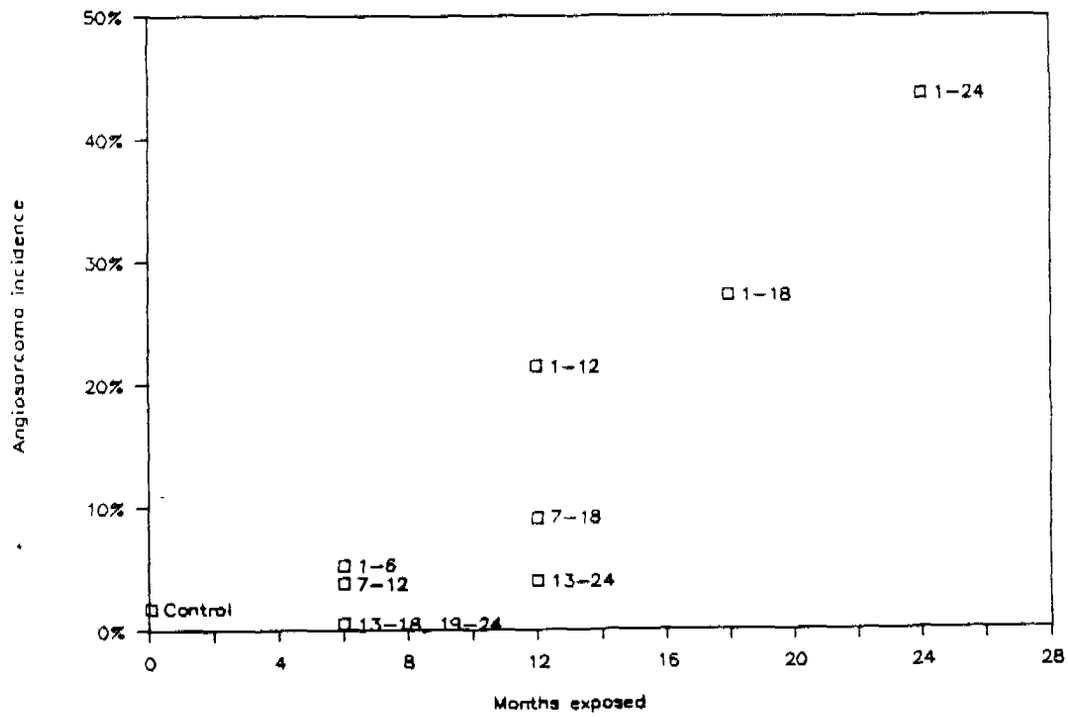


Fig. 1. Effect of duration and age at exposure on angiosarcoma incidence (from Drew et al., 1983).

Groups of female Fischer-344 rats, golden Syrian hamsters, B6C3F1 mice, and CD-1 Swiss mice inhaled vinyl chloride at 100 ppm for durations of 6, 12, 18, or 24 months beginning 0, 6, 12, or 18 months into the exposure period. (Prior to exposure, animals were 5–6 weeks old when received at the testing laboratory, then they were observed and weighed for 3 weeks.) Vinyl chloride caused angiosarcomas and mammary gland carcinomas in all four strains; in addition, there were hepatocellular carcinomas in rats, stomach adenomas and skin carcinomas in hamsters, and lung carcinomas in CD-1 Swiss mice. In general, cancer incidence increased with duration of exposure and decreased the later the age at first exposure. For example, Fig. 1 shows angiosarcoma incidence in each group of rats plotted against exposure duration; incidence increases with duration, and for the same duration incidence is higher for groups exposed earlier.

Maltoni et al. (1981) investigated the existence of dose-rate effects as part of a comprehensive vinyl chloride study. Groups of male and female Sprague–Dawley rats inhaled 6000 or 10000 ppm vinyl chloride for 100 h under different exposure schedules, three schedules beginning at 13 weeks of age and one schedule beginning at 1 day of age (4 h a day, 5 days a week, for 5 weeks). Fig. 2 shows that angiosarcoma incidence increased sharply in rats exposed from 1 day of age. Fig. 3 compares this angiosarcoma incidence (in the rats exposed for 5 weeks beginning at 1 day of age) to that of rats exposed for 52 weeks beginning at 13 weeks of age; the angiosarcoma incidence for rats exposed for 5 weeks as newborns is higher than that for rats exposed for 52

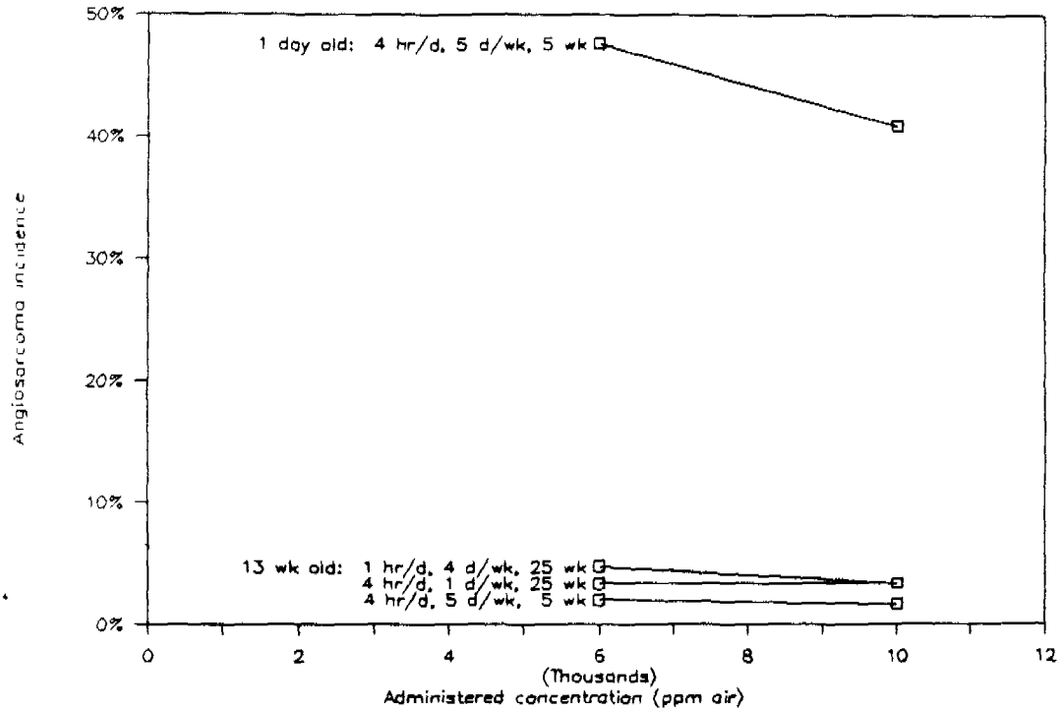


Fig. 2. Effect of age at exposure on angiosarcomas induced by 100-h exposures (from Maltoni et al., 1981, experiments BT10 and BT14).

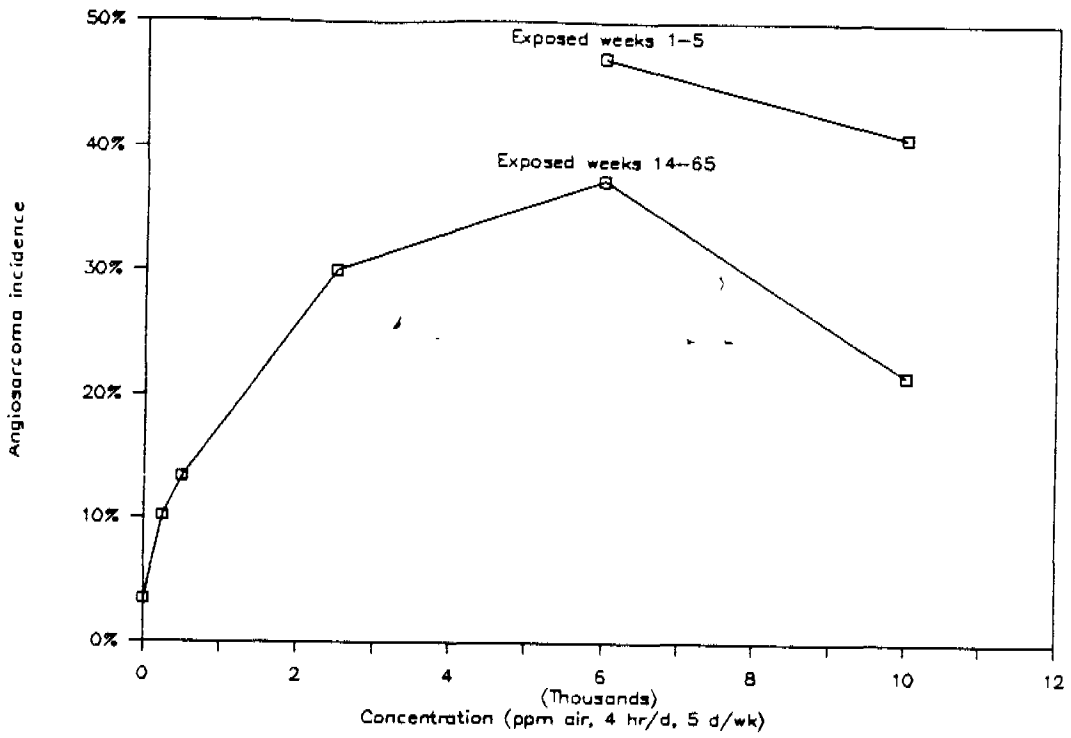


Fig. 3 Comparison of newborn and later-life exposure on angiosarcoma incidence (from Maltoni et al., 1981, experiments BT1 and BT14).

weeks after maturity. Further, hepatoma incidence, virtually nonexistent in rats exposed for 52 weeks after maturity, approaches 50% in rats exposed for 5 weeks as newborns.

Laib et al. (1985) studied the effect of age on induction by vinyl chloride of hepatic adenosine-5'-triphosphatase (ATPase)-deficient enzyme-altered foci, a putative precursor of hepatocellular carcinoma. Groups of newborn male and female Wistar rats inhaled 2000 ppm vinyl chloride for different periods of time; their livers were evaluated at 4 months. The investigators concluded that "the induction of pre-neoplastic hepatocellular lesions in rats by vinyl chloride is restricted to a well-defined period (approximately day 7 to 21) in the early lifetime of the animals." They attributed the lack of response in the first 5 days to the lack of hepatocellular proliferation and the low rate of vinyl chloride metabolism at this stage of development.

Further mechanistic investigations into the effect of age on vinyl chloride-induced DNA adducts has been studied by Fedtke et al. (1990).

## 3. Results

An empirical, quantitative approach is used to model early-life sensitivity to inhaled vinyl chloride, supplementing conventional approaches for estimating the increased cancer risk from lifetime exposure. A single estimate is not presumed to apply to the entire population at risk; instead, the new approach makes distinctions about the cancer risks for different population segments.

Fig. 1, where cancer incidence is higher for groups exposed earlier, suggests cancer incidence

might be modeled as a function of remaining lifetime. Cogliano and Parker (1992) analyzed the results of Drew et al. (1983) with an empirical model that approximates cancer risk as a bilinear function of dose and some power of remaining life. That is, let

$T$ be the lifespan, so $T - t$ is the remaining life at age $t$, and
$k$ be the exponent associated with remaining life.

Then for a dose $d$ received at age $t$, the incremental cancer risk is assumed proportional to $d(T - t)^k$.

Under this model, the effectiveness of each increment of dose depends on both the dose level $d$ and the age at exposure $t$. The incremental cancer risk would increase as either the dose $d$ increases or the age at exposure $t$ decreases. To evaluate the effectiveness of a particular exposure schedule, each increment of exposure can be weighted by the proportionality function $d(T - t)^k$ and summed accordingly; for example, if dosing is constant between ages $A$ and $B$, then the age-weighted exposure for the period of dosing is proportional to

$$d \int_A^B (T - t)^k \, dt$$

For full life exposure (between ages 0 and $T$), the age-weighted exposure is proportional to

$$d \int_0^T (T - t)^k \, dt$$

Expressed as a fraction of full-life exposure, the effectiveness of dosing between ages $A$ and $B$ is,

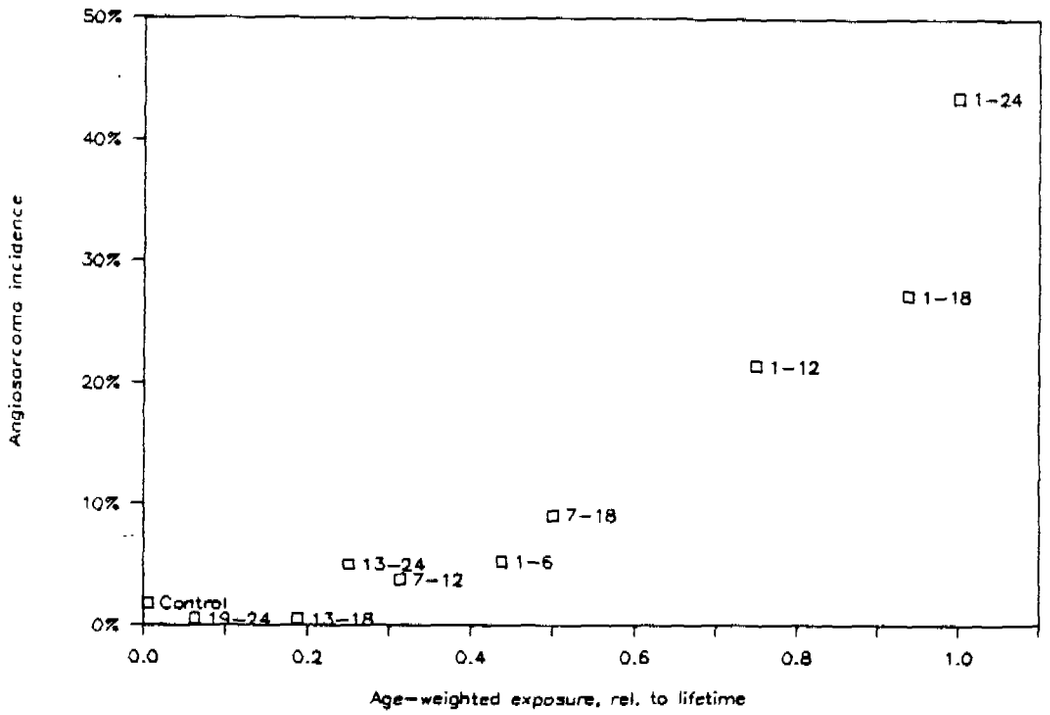


Fig. 4. Data from Fig. 1 replotted to show angiosarcoma incidence as a function of age-weighted exposure ($k = 1$) (from Drew et al., 1983).

therefore,

$$\int_A^B (T-t)^k \, dt \Big/ \int_0^T (T-t)^k \, dt$$

Cogliano and Parker (1992) provide a table showing, for a given duration $B - A$, how age-weighted exposure increases as the age at first exposure $A$ decreases or as $k$ increases above 0. Using age-weighted exposure for $k = 1$ instead of simple duration of exposure, Fig. 4 shows the results from Drew et al. (1983) that were plotted in Fig. 1. In Fig. 4, groups exposed earlier in life are shifted to the right, reflecting a higher age-weighted exposure, while groups exposed later are shifted left. The result resembles a more distinct dose-response curve, suggesting age-weighted exposure is useful in explaining the observed cancer incidences. Thus risk estimates are a function of exposure concentration, exposure duration, and age at exposure. Cancer risks from chronic exposure can be apportioned to different ages, with higher risks for exposure occurring at earlier ages.

These results suggest the potential for vinyl chloride to cause cancer is greatest for newborn exposure. Only the Maltoni et al. (1981) study provides direct information about this sensitive stage of development. Cogliano (1989, 1990) developed risk estimates from the results of Maltoni et al. (1981). The essential features of this analysis are, (a) the exposure periods in the early-life studies (weeks 1–5 for Maltoni et al. (1981), days 7–21 for Laib et al. (1985)) do not overlap those of the chronic studies (where exposure begins after 2–3 months), (b) the cancer risk from early-life exposure is roughly equal that from full-life exposure beginning after maturity, and (c) because the effects of early-life exposure are different from those of full-life exposure, early-life exposures are treated differently from exposures later in life. Thus, the risk of cancer from vinyl chloride is composed of two parts: a risk from chronic exposure occurring mostly after maturity, and a risk of similar size attributable to short-term, early-life exposure. This effectively doubles the vinyl chloride risk estimate that is derived from chronic studies. The estimate for chronic exposure can be apportioned throughout life according to a declining age-weighting curve described by Cogliano and Parker (1992), while a further risk would be incurred if exposure occurred early in life.

These assessments were considered by the U.S. and California Environmental Protection Agencies to guide their responses to indoor inhaled vinyl chloride in a housing development adjacent to a mixed-use landfill designated as a Superfund site. For cancer risks, a target risk range of 1 in 1 000 000 to 1 in 10 000 was used to determine whether action was taken at the site. Although there is no direct evidence of increased human sensitivity to vinyl chloride-induced carcino-

Table 1
Risk-based action levels for vinyl chloride

| Indoor air action level | Response | Risk criterion |
|---|---|---|
| < 0.2 ppb | No immediate action | Potential cancer risks from lifetime exposure and from 4-year childhood exposure within target risk range |
| 0.2–1 ppb | Interim (30-day) remediation | Potential lifetime cancer risk from 4-year childhood exposure is at upper end of target risk range |
| 1–25 ppb | Immediate (12-day) remediation | Potential lifetime cancer risk from 4-year childhood exposure exceeds target risk range |
| 25+ ppb | Immediate relocation offered | Potential risk of male reproductive toxicity from subchronic exposure |

genicity with exposure during childhood or adolescence, the animal evidence of such an age-dependent sensitivity was considered to be sufficient to warrant public health concern for young children potentially exposed to vinyl chloride. Therefore, cancer risks to young children became the risk focus for development of action levels at low vinyl chloride levels (Hiatt et al., 1994). Noncancer toxicity was also considered; at high exposures a reference dose for male reproductive toxicity could be exceeded (Hiatt et al., 1994). The risk-based action levels are described in Table 1.

## 4. Discussion

This analysis shows how several innovative study designs can provide information about early-life sensitivity that can be used in risk assessment. The lifetime cancer studies of Drew et al. (1983) and Maltoni et al. (1981), by including some animals with only early-life exposure, provide empirical evidence of enhanced sensitivity. The mechanistic studies of Laib et al. (1985) confirm the empirical evidence of early-life sensitivity. The consistent observation of angiosarcomas in lifetime animal and human occupational studies adds to the credibility of the results. By drawing on these different sources of information, confidence is enhanced in the risk assessment's conclusions.

Besides showing how these innovative study designs can be used in risk assessment, this analysis has implications for the interpretation of epidemiologic studies. Adults may not be the most sensitive population, and hence occupational studies, the predominant study in cancer epidemiology, may not identify hazards to children or other potentially sensitive subpopulations. Quantitative risk estimates based on workers may not be health-conservative for other populations. Management decisions based on worker studies may, thus, not afford the degree of protection anticipated.

There are also implications for study design. Valuable information can be provided by more investigations of the effects of timing of exposure, effects in immature animals, and epidemiologic studies outside occupational settings. The Maltoni et al. (1981) study design can provide empirical information to identify a potential for early-life sensitivity, and Laib et al. (1985) study shows how mechanistic research can confirm these empirical observations.

Perhaps the most pressing research need, however, is identifying other substances that affect sensitive stages of development. Screening studies need not be prohibitively expensive: the Maltoni et al. (1981) study demonstrates a protocol that can indicate whether newborns are especially susceptible. Valuable information can be gained from a group of animals exposed immediately after birth for a short time. This assessment has shown one way that such information can be analyzed and presented. With this or a similar approach, risk assessments can better identify susceptible individuals most at risk.

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