

Appendix D

A SUMMARY REVIEW OF CANCER DOSE-RESPONSE ANALYSES ON DIESEL EXHAUST

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D.1. INTRODUCTION

Several individuals and organizations have previously conducted dose-response assessments to estimate quantitatively the cancer risk from exposures to DE. Estimations were performed on the basis of either epidemiologic and/or experimental data. As concluded in Section 8.5, EPA finds that available epidemiologic data are too uncertain to confidently derive a unit risk estimate for DE-induced lung cancer, and that rat data are not suitable for estimating human risk. Nevertheless, a review of historical dose-response evaluations is provided here as background information. This information is not intended to constitute endorsement or a recommendation for use in quantitative risk assessment.

Early analyses to quantitatively assess the carcinogenicity of DE were hindered by a lack of positive epidemiologic studies and long-term animal studies. One means of overcoming these obstacles was the use of comparative potency methods based on combined epidemiologic and experimental data. By the late 1980s, the availability of dose-response data from animal bioassays and epidemiologic studies provided an opportunity for the derivation of both animal and human data-based estimates, although considerable uncertainties were generally acknowledged by the authors of these assessments.

D.2. COMPARATIVE POTENCY METHODS

In this method, the potency of diesel particulate matter (DPM) extract is compared with other combustion or pyrolysis products for which epidemiology-based unit risk estimates have been developed. Comparisons are made using short-term tests such as skin painting, mutations, and mammalian cell transformation. The ratio of the potency of DPM extract to each of these agents is then multiplied by their individual unit risk estimates to obtain the unit risk for DE. If epidemiology-based estimates from more than one pollutant are used, the derived potencies are generally averaged to obtain an overall mean. Major uncertainties of this method include the assumptions that (1) the cancer potency of DE can be determined on the basis of the relative effectiveness of the organic fraction alone; (2) the relative potency in short-term tests is an accurate predictor of lung cancer potency; and (3) DPM extracts are similar in chemical composition and proportion as combustion or pyrolysis products.

In the study by Albert et al. (1983), epidemiology-based unit cancer risk estimates for coke oven emissions, cigarette smoke condensate, and roofing tar were used. Samples of DPM were collected from three light-duty engines (a Nissan 220 C, an Oldsmobile 350, and a

Volkswagen turbocharged Rabbit), all run on a highway fuel economy test cycle, and from a heavy-duty engine (Caterpillar 3304) run under steady-state, low-load conditions. The DPM extracts were tested in a variety of assays. Dose/concentration-dependent increases in response were obtained for the four assays listed below:

- Ames *Salmonella typhimurium* (TA98) reverse mutation,
- Gene mutation in L5178Y mouse lymphoma cells,
- Sencar mouse skin tumor initiation test, and
- Viral enhancement of chemical transformation in Syrian hamster embryo cells.

Only the first three assays were used to develop comparative potency estimates because of variability of responses in the enhancement of the viral transformation assay. The in vitro studies were carried out both in the presence and absence of metabolic activators. The potency, defined as the slope of the dose-response curve, was measured for each sample in each short-term assay.

The skin tumor initiation test was positive for all the engines tested except the Caterpillar engine. Only the Nissan engine, however, resulted in strong dose-response data. Because skin tumor initiation was considered to be the most biologically relevant test, it was used to derive potency estimates for the Nissan engine. An estimate for the Nissan engine was then derived by multiplying the epidemiology-based potency estimates for each of the three agents (coke oven emissions, roofing tar, and cigarette smoke condensate) by the ratios of their potencies in the skin tumor initiation test to that of the Nissan diesel engine. According to this method, three 95% upper-bound estimates of lifetime cancer risk per microgram per cubic meter of extractable organic matter were derived for the Nissan diesel, based on potency comparisons with each of the three agents. These values are: coke oven emissions, 2.6×10^{-4} ; roofing tar, 5.2×10^{-4} ; and cigarette smoke condensate, 5.4×10^{-4} . The average of the three equals 4.4×10^{-4} .

The potency of the other diesel emission samples was not estimated directly because of the weak response in the skin tumor initiation test. Instead, their potency relative to the Nissan engine was estimated as the arithmetic mean of their potency relative to the Nissan in the *Salmonella* assay in strain TA98, the sister chromatid exchange assay in Chinese hamster ovary cells, and the mutation assay in mouse lymphoma cells. The estimated lifetime cancer risk per microgram per cubic meter of extractable organic matter for extracts from these engines are as follows: Volkswagen, 1.3×10^{-4} ; Oldsmobile, 1.2×10^{-4} ; and Caterpillar, 6.6×10^{-6} .

Harris (1983) developed comparative potency estimates for the same four engines used by Albert et al. (1983) but used only two epidemiology-based potency estimates: those for coke oven emissions and for roofing tar. He employed preliminary data from three of the same assays used by Albert et al. (1983): the Sencar mouse skin tumor initiation assay, enhancement of viral transformation in Syrian hamster embryo cells, and the L5178 mouse lymphoma test. The DE cancer potency estimates were then derived by multiplying the epidemiology-based cancer

1 potency estimates for both coke oven emissions and roofing tar by the ratio of their potencies
2 compared with DPM extract in each of the three bioassays. Harris (1983) derived an overall
3 mean relative risk value of 3.5×10^{-5} per $\mu\text{g}/\text{m}^3$ for the three light-duty engines with a 95% upper
4 confidence limit of 2.5×10^{-4} . Individual mean values for each engine were not reported.

5 McClellan (1986), Cuddihy et al. (1981, 1984), and Cuddihy and McClellan (1983)
6 estimated a risk of about 7.0×10^{-5} per $\mu\text{g}/\text{m}^3$ DPM using a comparative potency method similar
7 to those reported in the preceding paragraph. The database was similar to that used by Albert et
8 al. (1983) and Harris (1983).

10 **D.3. EPIDEMIOLOGY-BASED ESTIMATION OF CANCER RISK**

11 The first lung cancer risk estimates based on epidemiologic data were derived by Harris
12 (1983). He assessed the risk of exposure to DE using data from the London Transport Worker
13 Study reported by Waller (1981). Five groups of employees from the London Transport
14 Authority (LTA) were used: bus garage engineers, bus drivers, bus conductors, engineers in
15 central works, and motormen and guards. The first group was considered to have received the
16 highest exposure; the next two, intermediate; and the last two groups, none. When cancer death
17 rates for the high-exposure group were compared with those of London males, there was no
18 increase in the observed-to-expected (O/E) ratios. The author, in fact, considered the results to
19 be negative. However, because the low rate of lung cancer in all the LTA exposure groups may
20 have been the result of a “healthy worker” effect, Harris (1983) compared the exposed groups
21 with internal controls. He merged the three exposed groups and compared them with the two
22 groups considered to be unexposed. An adjustment was made for the estimated greater exposure
23 levels of garage engineers compared with bus drivers and conductors. Using this method, the
24 relative risk of the exposed groups was greater than 1 but was statistically significant only for
25 garage engineers exposed from 1950 to 1960. In that case, the O/E ratio was 29% greater than
26 the presumed unexposed controls.

27 Harris (1983) identified a variety of uncertainties relative to potency assessment based on
28 this study. These included:

- 29 • small unobserved differences in smoking incidences among groups, which could have a
30 significant effect on lung cancer rates;
- 31 • uncertainty about the magnitude of exposure in the exposed groups;
- 32 • uncertainty regarding the extent of change in exposure conditions over time;
- 33 • random effects arising from the stochastic nature of the cancer incidence; and
- 34 • uncertainty in the mathematical specification of the model.

1 Taking the uncertainties into account, he derived a maximum likelihood excess relative
2 risk estimate of 1.23×10^{-4} , with a 95% upper confidence limit of 5×10^{-4} per $\mu\text{g}/\text{m}^3$ DPM per
3 year.

4 McClellan et al. (1989) reported risk estimates based on the Garshick et al. (1987) case-
5 control study in which lung cancer in railroad workers was evaluated. Using a logistic regression,
6 the expected relative risk of lung cancer death was estimated to rise 0.016 per year of exposure to
7 DE. Adjustments were made to convert to continuous exposure (168 vs. 40 hours) for 70 years.
8 Because exposure levels could not be defined exactly, two sets of calculations were made,
9 assuming inhaled DPM concentrations of either 500 or 125 $\mu\text{g}/\text{m}^3$ DPM. The number of excess
10 cancer deaths per year in the United States was estimated to be 3,800 (95% C.I. 400-7400 when
11 an exposure of 125 $\mu\text{g}/\text{m}^3$ was used, and 950 (95% C.I. 100-1,900) when 500 $\mu\text{g}/\text{m}^3$ DPM was
12 used.

13 The California EPA (Cal-EPA, 1998) derived unit risk estimates for lung cancer based
14 upon the Garshick et al. (1987) case-control study and the Garshick et al. (1988) cohort study of
15 U.S. railroad workers. A variety of exposure patterns were considered, characterized by two
16 components: the average exposure concentration for the workers as measured by Woskie et al.
17 (1988) and the extent of change in exposure from 1959 to 1980. The lowest lifetime risk estimate
18 derived was 1.3×10^{-4} per $\mu\text{g}/\text{m}^3$ and the highest was 2.4×10^{-3} per $\mu\text{g}/\text{m}^3$. The geometric mean
19 was 6×10^{-4} per $\mu\text{g}/\text{m}^3$.

20 Steenland et al. (1998) estimated lung cancer risk of truck drivers on the basis of a case-
21 control study of decedents in the Teamsters Union (Steenland et al., 1990). Retrospective
22 exposure estimates were made starting with a set of 1990 exposure measurements for different
23 job categories and then retrospectively estimating from 1982 to about 1950 using various factors,
24 including diesel vehicle miles traveled and engine emission rates per mile. The 1990 job category
25 estimates came from an extensive industrial hygiene survey of elemental carbon (EC) exposures in
26 the trucking industry by Zaubst et al. (1991). Lifetime (through age 75) excess risk of lung cancer
27 death for male truck drivers was calculated with the aid of a cumulative exposure model.
28 Assuming a most likely emissions scenario of 4.5 g/mile in 1970, and a 45-year exposure to 5
29 $\mu\text{g}/\text{m}^3$ of EC beginning at age 20 and ending at age 65, the estimated excess lung cancer risk was
30 determined to be 1.6% (95% CI 0.4%-3.1%). Using the same data base, Stayner et al (1998)
31 presented an estimate of excess lifetime risk of $4.5\text{E-}4$ for a worker exposed to 1 $\mu\text{g}/\text{m}^3$ of DE
32 for 45 years.
33

1 **D.4. ANIMAL BIOASSAY-BASED CANCER POTENCY ESTIMATES**

2 With the availability of chronic cancer bioassays, a considerable number of potency
3 estimates were derived using lung tumor induction in rats. A high degree of uncertainty exists in
4 the use of the rat data to predict human risk. Major uncertainties include: (1) differences in
5 particle deposition patterns between rats and humans, (2) differences in sensitivity between rats
6 and humans to the carcinogenic action of DE, and (3) extrapolation of rat lung tumor responses at
7 high concentrations to ambient concentrations without a clear understanding of the mode of
8 action of DE. It is now widely recognized that the rat lung tumor response associated with any
9 insoluble particles at high concentrations is mediated by a particle-overload mechanism (ILSI,
10 2000), suggesting that rat data for DE are not suitable for estimating human risk at low
11 environmental concentrations.

12 The first risk estimate was reported by Albert and Chen (1986), based on the chronic rat
13 bioassay conducted by Mauderly et al. (1987). Using a multistage model and assuming equivalent
14 deposition efficiency in humans and rats, they derived a 95% upper confidence limit of 1.6×10^{-5}
15 for lifetime risk of exposure to $1 \mu\text{g}/\text{m}^3$. Pott and Heinrich (1987) also used a linear model and
16 data reported by Brightwell et al. (1989), Heinrich et al. (1986), and Mauderly et al. (1987).
17 They reported risk estimates ranging from 6×10^{-5} to 12×10^{-5} per $\mu\text{g}/\text{m}^3$. Smith and Stayner
18 (1990), using time-to-tumor models based on the data of Mauderly et al. (1987), derived point
19 (MLE) estimates ranging from 1.0×10^{-4} to 2.1×10^{-4} per $\mu\text{g}/\text{m}^3$ after converting from
20 occupational to environmental exposure scenario.

21 Pepelko and Chen (1993) developed unit risk estimates based on the data of Brightwell et
22 al. (1989), Ishinishi et al. (1986), and Mauderly et al. (1987) using a detailed dosimetry model to
23 extrapolate dose to humans and a linearized multistage (LMS) model. Taking the geometric mean
24 of individual estimates from the three bioassays, they derived unit risk estimates of 1.4×10^{-5} per
25 $\mu\text{g}/\text{m}^3$ when dose was based on carbon particulate matter per unit lung surface area rather than
26 whole DPM, and 1.2×10^{-4} per $\mu\text{g}/\text{m}^3$ when based on lung burden per unit body weight.

27 Hattis and Silver (1994) derived a maximum likelihood estimate for occupational exposure
28 of 5.2×10^{-5} per $\mu\text{g}/\text{m}^3$ based on lung burden and bioassay data reported by Mauderly et al.
29 (1987) and use of a five-stage Armitage-Doll low-dose extrapolation model. California EPA
30 (CAL-EPA, 1998) derived a geometric mean estimate of 6×10^{-5} per $\mu\text{g}/\text{m}^3$ from five bioassays
31 using an LMS model.

32 To demonstrate the possible influence of particle effects as well as particle-associated
33 organics, an additional modeling approach was conducted by Chen and Oberdorster (1996).
34 Employing a biologically based two-stage model and using malignant tumor data from Mauderly
35 et al. (1987), the upper-bound risk estimate for exposure to $1 \mu\text{g}/\text{m}^3$ was estimated to be

1 1.7×10^{-5} . This estimate is virtually identical to that using the LMS model, assuming
2 nonthreshold effect of particles. If a threshold of particle effect is assumed, however, the
3 estimated risk decreases about fivefold. The results also show that the mechanism of DE-induced
4 lung tumor at high exposure concentrations may differ from that at low exposure concentrations,
5 with the organics and particles playing primary roles of tumorigenesis, respectively, at low and
6 high concentrations. Overall, the potency estimates on the basis of animal bioassays are in the
7 range of 10^{-6} to 10^{-4} per $1 \mu\text{g}/\text{m}^3$ of DPM. Valberg and Crouch (1999)
8 conducted a meta-analysis of rat bioassays by pooling together data of low-dose groups from
9 different bioassays. There are eight bioassays used in the meta-analysis; half of them had duration
10 of 24 months, and the remaining studies had duration of 30 months or more. Animals with
11 continuous lifetime exposure of less than $600 \mu\text{g}/\text{m}^3$ of DE were included in the analysis.
12 Continuous lifetime exposure is calculated by protracting actual DE exposure to 30 months (24
13 hours per day, 7 days per week). The researchers concluded that exposure of rats to DE at
14 concentrations not associated with lung overload is consistent with no tumorigenic effect.
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