CARCINOGEN ASSESSMENT GROUP'S
PRELIMINARY REPORT ON
POPULATION RISK TO AMBIENT COKE OVEN EXPOSURES

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Introduction and Summary

As requested in a memo from Joseph Padgett dated April 5, 1977 the CAG has done an analysis of the possible excess lung cancer risk in populations living in the vicinity of coke ovens. There is very substantial epidemiological evidence that exposure to coke oven emissions can induce an excess risk of cancer in workers engaged in the production of coke or in the manufacture of coal gas. This excess risk is mainly due to a higher than expected death rate from lung cancer and to a much lesser extent from a higher than expected death rate from cancers of the bladder, prostate, pancreas and large intestine.

There are major difficulties in predicting the cancer risk to populations living in the vicinity of coke ovens. The chemical composition of emissions from coke ovens is exceedingly complex. These effluents do contain known carcinogens, particularly those belonging to the class of polycyclic organics. However, by analogy with cigarette smoke, the overall carcinogenic effect of the mixture may be greater than that ascribible to identified carcinogens. As the emissions move away from the coke ovens, it is possible that the chemical composition and the associated carcinogenic potency of the material may change significantly. The best that can be done under the circumstances is to use an indicator such as benzene-soluble organics (BSO) as a guide to the exposure of populations living near coke ovens. Unfortunately, there are no animal inhalation studies with coke oven emissions and consequently no evidence on the extent to which dilution and aging of emissions affects its carcinogenic potential or the most appropriate indicator to use for carcinogenic effect.

Furthermore, there are no epidemiological studies of the cancer exposure of populations living near coke ovens or gas works as a basis for estimating the magnitude of the excess cancer risk, although such studies would necessarily provide only a crude measure of the carcinogenic effects of coke oven emissions.

In the analysis presented here, we have used the data from a series of studies by Lloyd, Redmond, Mazumdar and co-workers (1-4) on cancer mortality in relation to BSO exposure in coke oven workers and other workers in the steel industry. This epidemiological dose-response data for lung cancer is extrapolated on the basis of a linear non-threshold, dose-response relationship to provide estimates of the excess risk of lung cancer in populations living at various distances from coke ovens. The exposure estimates and the size of the population groups are taken from an assessment by the Stanford Research Institute (7). The validity of the exposure assessment is outside the CAG's purview.

The risk assessment for lung cancer is summarized in Table 4. The number of people exposed to coke oven emissions is on the order of fifteen million. About fourteen million people have a lifetime excess lung cancer risk of about 6 chances in 10,000. About one million have a lifetime excess lung cancer risk of 1 chance in 1,000. The remaining 100,000 people have a lifetime excess lung cancer risk which ranges from about 2 chances in a 1000 to 6 chances in 1000 depending on where they live. Without any significant coke oven exposure, the lifetime chance of dying of lung cancer is 3.29%. For the 100,000 highest exposed people, there is a 0.2% to 0.6% excess chance of dying of lung cancer. For the rest of the 15 million people the excess is about 0.1%. The total number of excess lung cancer deaths is about 150 cases per year.

These estimates should be regarded as crude and probably conservative; i.e., on the high side.

Estimated Risk Models Based on Steel Workers' Exposure to Coke Oven Emissions

A series of studies by Lloyd, Redmond, Mazumdar, and co-workers[1-4] has established a strong relationship between the total exposure to coke oven emissions and an increased risk of death due to lung cancer.

Land[5] in an OSHA hearing on coke oven standards used the most up-to-date summary of the data based on the cited studies to estimate risk to coke oven workers. These data were supplied to EPA and were further summarized and adjusted in a manner shown and explained in Table 1.

These data represent changing exposures to individuals over segments of their life spans with an observation of mortality over a different and, at least, partially overlapping additional segment of their life spans. From this fragmented type of data, we wish to predict the effect of a constant exposure over the individual's entire life span to the probability of the individual's ultimate death being due to lung cancer.

Weibull Model

To obtain a lifetime probability estimate, it is necessary to relate the "instantaneous probability" of death due to lung cancer to exposure and age. Following Armitage and Doll[6] we assume that the instantaneous probability of death may be expressed as

$$h_2(t) = \gamma(\alpha + \beta x^m) t^{\gamma-1}$$

where t is the age of the individual, x is the level of exposure, and γ, α, β and m are unknown parameters to be estimated from the data shown in Table 1.

The parameters were estimated using weighted nonlinear least squares where the weights were taken equal to the person-years of observation. This resulted in estimates

$\gamma = 3.76984$

$\alpha = .27750 \times 10^{-8}$

$\beta = .19248 \times 10^{-10}$

$m = 1.21110$

Often for theoretical reasons the parameter m is taken as an integer, giving an approximate "m-hit" model. If we restrict m = 1, the best fitting integer, we have

$\gamma = 4.32324$

$\alpha = .2142 \times 10^{-9}$

$\beta = .63192 \times 10^{-11}$

In Appendix I the lifetime risk of lung cancer and the expected lifespan were derived, giving

$$Q_2(\infty) = \frac{(\alpha + \beta x^m)}{(\alpha + \beta x^m + \rho^\gamma)} = \frac{\dfrac{\alpha}{\alpha + \rho^\gamma} + \dfrac{\beta x^m}{\alpha + \rho^\gamma}}{1 + \dfrac{\beta x^m}{\alpha + \rho^\gamma}}$$

and

$$E = \frac{\Gamma(1 + 1/\gamma)}{(\alpha + \beta x^m + \rho^\gamma)^{1/\gamma}},$$

respectively. The only unknown term is ρ^γ, the term for non-lung-cancer deaths. We can estimate ρ^γ in the following manner. The median survival time may be expressed as t_m where

$$1/2 = e^{-(\alpha + \beta x^m + \rho^\gamma) t_m^\gamma}$$

or

$$\rho^\gamma = \frac{\ln(2)}{t_m^\gamma} - (\alpha + \beta x^m) ,$$

where x is, in this case, the national average ambient exposure. In the SRI Report[7] on coke oven exposure, it is estimated that the BSO levels are:

4.20 in cities containing coke ovens

3.75 in cities not containing coke ovens

.95 in rural areas

Assuming a locational distribution of the average American of 10%, 65% and 25%, respectively, in the three areas, the national average is estimated as x = 4.2(.1) + 3.75(.65) + .95(.25) = 3.095, so that

$$\rho^\gamma = \frac{\ln(2)}{65.36^\gamma} - [\alpha + \beta(3.095)^m] ,$$

where 65.36 is the median life span of the U.S. nonwhite male based on 1971 Vital Statistics.[8] The term ρ^γ is estimated to be 9.60347×10^{-9}, when m = 1, and 9.65501×10^{-8} when m = 1.2111.

Substituting the estimated parameters into the risk and expected lifetime equations, we obtain the results shown in Table 2, column 1.

However, this equation is really strictly applicable only to a small subset of the U.S. population, namely the black northern male who was healthy enough to have a physically demanding job such as that of a steel worker. This is true since these are essentially the characteristics that the sample of workers in the epidemiological study possesses. In making a prediction about the effect of coke oven emissions on the U.S. population in general, one can either use the equation based on this highly nonrandom sample or attempt to extrapolate the equation in some reasonable manner to the U.S. population.

Method for Adjusting Equations for One Population to Apply to Another

For small exposures, x, the lifetime probability of a tumor may be expressed as

$$Q_2(\infty) \simeq \frac{\alpha}{\alpha + \rho^{\gamma}} + \frac{\beta x^m}{\alpha + \rho^{\gamma}} .$$

In this case the relative ratio of total to "non-BSO-caused" tumors can be obtained by dividing $Q_2(\infty)$ by $\alpha/(\alpha + \rho^{\gamma})$, giving

$$R \simeq 1 + \frac{\beta x^m}{\alpha} .$$

If we assume that this ratio is constant between race-sex-region, etc., then

$$\frac{\beta}{\alpha} = \frac{\beta_n}{\alpha_n} = \theta ,$$

where β_n and α_n are national rates. If we denote the national rate as $Q_n(\infty)$ due to national average exposure of x_n, we have that

$$Q_n(\infty) = \frac{\alpha_n + \beta_n x_n^m}{\alpha_n + \beta_n x_n^m + \rho_n^\gamma} = \frac{1 + \theta x_n^m}{1 + \theta x_n^m + \rho_n^\gamma/\alpha_n} .$$

The term $Q_n(\infty)$ can be calculated from Vital Statistics by the segmented model discussed in Appendix I. Assuming $Q_n(\infty)$ to be known, we solve for the unknown

$$s = \frac{\rho_n^\gamma}{\alpha_n} = \left(\frac{1}{Q_n(\infty)} - 1\right)\left(1 + \theta x_n^m\right) .$$

Thus the adjusted lifetime probability of an individual randomly selected from the U.S. population exposed to a level x of BSO may be written as

$$Q_2(\infty) = \frac{1 + \theta x^m}{1 + \theta x^m + s} = \frac{\frac{1}{1+s} + \frac{\theta x^m}{1+s}}{1 + \frac{\theta x^m}{1+s}} .$$

Using 1971 Vital Statistics for total U.S. population, ICD Code 160-163, for respiratory system cancer rates, we calculated that $Q_n(\infty)$ = .0343. However, since lung cancer ICD 162 makes up only a fraction, 68,617/72,898 = .9413, of the total respiratory cancer in 1971, the adjusted rate is estimated to be $Q_n(\infty)$ = .0343 x .9413 = .0323. Thus we estimate $s = (.0323^{-1} - 1)(1 + 3.095^m\theta)$, and the equations for the national average are obtained by substitution of the appropriate terms and are shown in Table 2, column 2.

Under the assumption that the fraction (E_n) of total average life span lived, given the same exposure, is the same for black males and the total general population, we have that

$$E = E_n(\alpha + \beta x_n^m + \rho^\gamma / \alpha + \beta x^m + \rho^\gamma)^{1/\gamma}$$

where x_n is 3.095 and E_n is calculated to be 70.96. The expected life span equations are derived by substituting the appropriate numerical values into the equations and are shown in Table 3.

Effects of Coke Oven Emissions on U.S. Population

In the recent SRI Report, exposure of the U.S. population to coke oven emissions was estimated. The number of people in an exposure gradient is given in columns 1 and 2 in Table 4 and is taken from the SRI Report. The lifetime probability and the average length of life are also shown in Table 4, based on the equations in Tables 2 and 3 where the case m = 1, general U.S. population, was used. The other terms were obtained by simple arithematic in an obviously straightforward manner, where length of a life span is assumed to be 70.96 years. It is estimated that about .2% of all lung cancer deaths per year are due to coke oven emissions.

It would be possible to generate tables similar to Table 4 using the other three equations; however, the results would be only marginally different.

One potential criticism of the use of the Weibull Model is that, unlike other types of cancer, the lung cancer rates have a tendency to flatten out or even drop for older ages. However, while this does appear to be the case in the low exposure groups, it does not in the highly exposed group. Also as noted by Cook, et al.[9] this flattening appears to be explainable by a nonuniform historical exposure to environmental carcinogens and could be expected to follow the power law in the future if exposures were constant.

A potential method that could be used to overcome this difficulty is to assume that the total lung cancer rates, $h_2(t)$, are made up of two components: α_t, a rate of an age cohort which is not Weibull; and θ_t, which is. We write

$$h_{2t} = \alpha_t + \theta_t = \alpha_t + \gamma\beta x^m T_t^{\gamma-1}$$

where α_t is the nonexposed rate for the t^{th} interval and T_t is the average age of individuals in the t^{th} interval. We are given the rates

$$r_t = \alpha_t + \gamma\beta(3.095)^m T_t^{\gamma-1}$$

from 1971 Vital Statistics tables so that we estimate

$$\alpha_t = r_t - \gamma\beta(3.095)^m T_t^{\gamma-1} ,$$

and the total rates given an environmental exposure of x are

$$h_{2t} = r_t + \gamma\beta T_t^{\gamma-1}(x^m - 3.095^m) .$$

Using the constant segmented model discussed in Appendix I, the increased lifetime probability where $x = 10.9$, $m = 1$, total U.S. population, is calculated to be 6.7×10^{-3}. This is very close to 6.04×10^{-3}, the value calculated for the full Weibull model. Thus it does not appear that the fall of cancer rates for high age groups has a major impact on overall lifetime probability of lung cancer.

TABLE 1

SUMMARIZED DATA OF STEEL WORKER EXPOSURE TO COKE OVEN EMISSIONS

Defined Age at Entry	Group Dose Range[a]	Lung Cancer Rate/Year x 10^5	Person-years of Observation	Average Age During Observation Period[b]	Lifetime Average Exposure to BSO[c]
25-34	Not exposed	13.4	22,045	36.4	4.2
	0-99	31.2	3,202	35.1	20.5
	100-199	0	2,658	36.0	67.2
	200-299	99.0	3,030	36.3	109.1
	300+	130.6	3,062	37.7	160.5
35-44	Not exposed	24.7	16,277	46.3	4.2
	0-149	0	2,388	45.2	28.4
	150-299	67.2	2,976	46.1	82.3
	300-499	110.0	2,727	46.1	130.1
	450+	246.7	2,027	47.4	201.5
45-54	Not exposed	150.4	11,306	55.8	4.2
	0-249	65.5	1,527	55.3	47.9
	250-449	234.5	1,706	55.9	107.4
	450-699	258.9	1,545	56.0	169.4
	700+	601.5	1,330	56.2	263.3
55-69	Not exposed	70.0	5,713	64.9	4.2
	0-249	203.7	491	65.6	43.7
	250-449	167.8	596	64.9	89.8
	450-749	558.7	716	64.5	160.5
	750+	2,222.2	450	65.9	681.7

[a]Units are the sum, for all jobs, of the products of the mg/m^3 of BSO in the air associated with the job and the length of time in months worked at the job.

[b]The term t is the average age at the start of the observation period + 1/2 total years observed ÷ total number of individuals alive at the start of the observation period.

[c]The term x is the total mg/m^3-months ÷ total months lived by the end of the observation period · fraction of year spent on the job + 4.2 = the background BSO levels in cities containing coke ovens. Units are μgm/m^3 BSO.

TABLE 2

LIFETIME PROBABILITY OF LUNG CANCER GIVEN AVERAGE EXPOSURES OF x $\mu gm/m^3$ OF BSO

Case	Population	
	Black-Urban-Male	General U.S. Population
m = 1	$\frac{.02164 + .0006438x}{1 + .0006438x}$	$\frac{.02966 + .0008824x}{1 + .0008824x}$
m = 1.2111	$\frac{.02794 + .0001938x^{1.2111}}{1 + .0001938x^{1.2111}}$	$\frac{.03147 + .0002183x^{1.2111}}{1 + .0002183x^{1.2111}}$

TABLE 3

EXPECTED AVERAGE LIFE SPAN GIVEN AVERAGE LIFETIME EXPOSURE TO x $\mu gm/m^3$ OF BSO

Case	Population	
	Black-Urban-Male	Total U.S. Population
m = 1	$\frac{109.907}{(9.81589 + .0063192x)^{.23131}}$	$\frac{120.408}{(9.81589 + .0063192x)^{.23131}}$
m = 1.2111	$\frac{119.663}{(9.93251 + .0019248x^{1.2111})^{.26526}}$	$\frac{130.492}{(9.93251 + .0091248x^{1.2111})^{.26526}}$

TABLE 4- ESTIMATED EFFECTS OF COKE OVEN EMISSIONS ON U.S. POPULATION UNDER WEIBULL PROBABILITY MODEL WHERE "HIT PARAMETER" m=1 AND ADJUSTMENTS FOR TOTAL POPULATION RATES USED

X = Exposure to BSO in µgm/m^3 In Air	Number of People in Exposure Group	Lifetime Probability of Lung Cancer	Increase In Lung Cancer Due to Coke Oven Emissions	Given Coke Oven Emissions Caused Lung Cancer Average Yrs. of Lifespan Lost	No. of Lung Cancer Death/Yr. Due To Coke Oven Emissions
Background=3.75	-----------	.03286	---------	-----------	---------
4.50	13,900,000	.03350	6.37×10^{-4}	12.34	125.0
5.50	1,034,000	.03435	1.49×10^{-3}	12.36	22.0
6.50	54,000	.03519	2.33×10^{-3}	12.39	1.8
7.50	7,780	.03604	3.18×10^{-3}	12.41	.4
8.50	2,420	.03689	4.02×10^{-3}	12.43	.1
10.90	1,800	.03890	6.04×10^{-3}	12.44	.2

Total=149.5/Yr.

References:

1. Lloyd J.W., Lundin F.E. Jr., Redmond C.K. al.: Long term mortality study of steel workers. IV. Mortality by work area. J. Occup. Med. 12: 151-157. 1970

2. Lloyd J.W.: Long term mortality study of steelworkers. V. Respiratory cancer in coke plant workers. J. Occup. Med. 13: 53-68. 1971

3. Redmond C.K., Ciocco A., Lloyd J.W., and Rush H.W.: Long-term mortality study of steelworkers. VI. Mortality from malignant neoplasms among coke oven workers. J. Occup. Med. 14: 621-629. 1972

4. Mazumdar S., Redmond C.K., Sollecito W. and Sussman N.: An epidemiological study of exposure to coal tar pitch volatiles among coke oven workers. J. Air Pollution Control Assn. 25: 382-389. 1975

5. Land C.E.: Presentation for OSHA hearings on coke oven standards, May 4, 1976

6. Armitage, P. and Doll R: The age distribution of cancer and a multi-stage theory of carcinogensis. British J. Cancer, Vol 18: 1-12, 1954

7. SRI draft report by Suta B.E.: Human population exposures to coke oven atmospheric emissions, June 1977

8. U.S. Dept. of Health, Education and Welfare: Vital Statistics of the United States, 1971, Vol. II--Mortality, Part A. Supt. of Documents, U.S. Govt. Printing Office. Stock No. 017-022-00378-3

9. Cook P.J., Doll R and Fellingham S.A.: A mathematical model for the age distribution of cancer in man, Int. J. Cancer, 4 (1969), pp 93-112

COKE OVENS

APPENDIX I

ESTIMATION OF LIFETIME RISK OF DEATH AND YEARS OF LIFE LOST DUE TO A SPECIFIC CAUSE

General Approach

The estimation of the lifetime probability of a disease in the presence of competing causes of death and the resulting life-shorting of the disease is a problem that has received considerable attention. Chiang (1968, pp. 242-68) has given a general solution to the problem using standard methods in competing risk analysis. Gail (1975), using these methods, derives explicit "figures of merit" for measuring the benefit of reduced exposure to environmental carcinogens.

Following Gail, we define the following functions:

$$S_1(t) = P\{\text{survive to} \geq t / c_1 \text{ is only cause of death}\}$$
$$S_2(t) = P\{\text{survive to} \geq t / c_2 \text{ is only cause of death}\},$$

where c_1 and c_2 make up all causes of death. The hazard function or age-specific or instantaneous death rate is denoted as $h_1(t)$, $h_2(t)$, respectively, for causes of death c_1 and c_2. Under the usual assumptions of independence of c_1 and c_2 the total probability of survival until time t and the total hazard from both causes are: $S(t) = S_1(t)S_2(t)$, $h(t) = h_1(t) + h_2(t)$, respectively and

$$S(t) = e^{-\int_0^t h(u)du} .$$

It can be readily shown that the lifetime probability of dying of cause c_2 is

$$Q_2(\infty) = \int_0^\infty h_2(t)S(t)dt$$

and the expected survival time or lifetime is

$$E = \int_0^\infty S(t)h(t)tdt.$$

Thus, given the specific functions $h_1(t)$, $h_2(t)$, the quantities of interest $Q_2(\infty)$ and E can be readily derived.

For two common assumptions concerning the form of $h_1(t)$, $h_2(t)$, the terms $Q_2(\infty)$, E are obtained in the next two sections.

<u>Constant Segmented Model</u>

Often the hazard or age-specific death rate is assumed to be constant over different time intervals but to change at interval boundaries. Formally, let us assume the entire life span is broken up into m mutually exclusive segments or intervals and the hazard functions are defined as follows:

Time Interval	$h_1(t)$	$h_2(t)$	$h(t)$
$0 - t_1$	α_{11}	α_{12}	α_1
$t_1 - t_2$	α_{21}	α_{22}	α_2
$\vdots$	$\vdots$	$\vdots$	$\vdots$
$t_{j-1} - t_j$	α_{j1}	α_{j2}	α_j
$\vdots$	$\vdots$	$\vdots$	$\vdots$
$t_{m-1} - \infty$	α_{m1}	α_{m2}	α_m

This is the situation where age-specific rates are estimated from narrow age intervals of typically 1 to 10 years.

In this case, the function $S(t)$, $t_{j-1} \leq t \leq t_j$, is

$$S(t) = S(t_{j-1}) \cdot e^{-\int_0^{t-t_{j-1}} \alpha_j du} = e^{-\left[(t-t_{j-1})\alpha_j + \sum_{k=1}^{j-1} (t_k - t_{k-1})\alpha_k\right]}$$

so that

$$Q_2(\infty) = \sum_{j=1}^{m} S(t_{j-1}) \int_{t_{j-1}}^{t_j} \alpha_{2j} e^{-(t-t_{j-1})\alpha_j} dt$$

$$= \sum_{j=1}^{m} S(t_{j-1}) \left[1 - e^{-(t_j - t_{j-1})\alpha_j}\right] \alpha_{2j}/\alpha_j \ .$$

This lifetime probability may be viewed intuitively as the sum of the probability of m mutually independent events, namely of dying of the specified disease in the specified time interval. Each of these m probabilities is the product of three probabilities:

1. Probability of death due to cause c_2 given that death occurred in the j^{th} time interval:

$$P_{1j} = \alpha_{2j}/\alpha_j \ ;$$

2. Probability of death between time t_j and t_{j-1} given survival up to time t_{j-1}:

$$P_{2j} = 1 - e^{-(t_j - t_{j-1})\alpha_j} \ ; \text{ and}$$

3. Probability of survival until time t_{j-1}:

$$P_{3j} = S(t_{j-1}) = \prod_{k=1}^{j-1} (1-P_{2k}) = e^{-\sum_{k=1}^{j-1}(t_k - t_{k-1})\alpha_k} .$$

By definition it follows that $P_{31} = 1$, $P_{2m} = 1$, and

$$Q_2(\infty) = \sum_{j=1}^{m} P_{1j}P_{2j}P_{3j} .$$

The expected life span under the segmented model may be expressed as

$$E = \sum_{j=1}^{m} S(t_{j-1}) \int_{t_{j-1}}^{t_j} \alpha_j e^{-(t-t_{j-1})\alpha_j} (t-t_{j-1})dt$$

$$= \sum_{j=1}^{m} S(t_{j-1}) \left(1 - e^{-(t_j-t_{j-1})\alpha_j}\right)/\alpha_j = \sum_{j=1}^{m} P_{2j}P_{3j}/\alpha_j$$

$$= \sum_{j=1}^{m} P_{1j}P_{2j}P_{3j}/\alpha_{2j} .$$

Weibull Model

Doll (1972) and others have pointed out that the Weibull distribution often fits time- and dose-dependent carcinogen response data. One form of a generalized Weibull model is to assume that

$$h_2(t) = \gamma(\alpha + \beta x^m)t^{\gamma-1} ,$$

where t is the age of the individual, x is the level of exposure to a carcinogen and γ, α, β, m are unknown parameters to be estimated from the data. If we make the additional simplifying assumption that the noncancer cause of death c_1 is also Weibull in form with common parameter γ, then

$$h_1(t) = \gamma\rho^{\gamma} t^{\gamma-1}$$

and the quantities of interest are

$$Q_2(\infty) = \int_0^{\infty} \gamma(\alpha + \beta x^m) t^{\gamma-1} e^{-(\alpha + \beta x^m + \rho^{\gamma}) t^{\gamma}}$$

$$= (\alpha + \beta x^m)/(\alpha + \beta x^m + \rho^{\gamma})$$

and

$$E = \int_0^{\infty} \gamma(\alpha + \beta x^m + \rho^{\gamma}) t^{\gamma} e^{-(\alpha + \beta x^m + \rho^{\gamma}) t^{\gamma}} dt$$

$$= \Gamma(1 + 1/\gamma)/(\alpha + \beta x^m + \rho^{\gamma})^{1/\gamma} .$$

References:

1. Chiang, C.L.: Introduction to Stochastic Processes in Biostatistics. New York: John Wiley, 1968

2. Doll, R.: The age distribution of cancer: Implications for model of carcinogenesis. J. Roy. Stat. Soc. A 134: 133-166, 1971

3. Gail, M.: Measuring the benefit of reduced exposure to environmental carcinogens. J. Chron. Dis. 28: 135-147, 1975