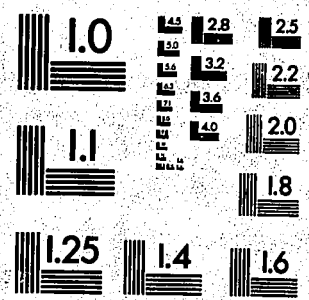
IMAGE EVALUATION TEST TARGET QA-3



150mm

6"

APPLIED IMAGE, Inc
1653 East Main Street
Rochester, NY 14609 USA
Phone: 716/482-0300
Fax: 716/288-5989

ST333

NIOSH-00228292

NIOSH

Comments to DOL

February 7, 1992

Ms. Caroline Freeman
Health Standards Program
Occupational Safety and Health
Administration
Room N-3669
200 Constitution Avenue, N.W.
Washington, D.C. 20210

Dear Ms. Freeman:

Per your request, enclosed is a table summarizing our risk estimates from fitting the multistage model to our cadmium cohort study. These risk estimates were intermediate between the estimates that we derived from fitting the Cox and Poisson regression models.

You should also note that our risk estimates from the Cox and Poisson models are approximately 50% higher than the estimates in our risk assessment report that we previously submitted to the docket on cadmium (H-057a). Dr. Kenneth Crump has suggested to us that lifetime risk should be calculated over the entire lifespan rather than the median lifespan (i.e., 75 years of age). We agree with this suggestion and have thus modified the program that was provided to us by Elizabeth Grossman to calculate excess risk up to the age 100 using the following formula:

$$\sum_{i=20}^{99} (RR_i - 1)\, q_1(i) \exp\left[-\sum_{j=20}^{i} \left((RR_j - 1) q_1(j) + q_a(j) \right) \right]$$

Where RR_i is the rate ratio estimate from the model, $q_1(i)$ represents the background age specific lung cancer rate, $q_a(i)$ represents the background age specific mortality for all causes, and i indexes age.

While modifying this program we also noticed that respiratory cancer rates, rather than lung cancer rates, had been mistakenly used. Therefore, we have also modified the program to use lung cancer rates and this also had some influence on the changes in our risk estimates.

Regarding the multistage model, our approach is based upon an approximation that has been used for epidemiologic studies (Whittemore and Keller, 1978). Although this approach has been previously used with Poisson regression (Mazumdar et al., 1989, Risk Analysis, Vol. 9(4), 551-563, 1989), we have adapted this approach to fitting the Cox proportional hazards model. Enclosed with this letter is an outline of the mathematical derivation for this method.

We assumed a 5 stage model for our analysis, since this is the number of stages that has generally been observed in other multistage analyses of lung cancer (e.g. smoking). We fit the model varying the stage affected by cadmium exposure and found that the model fit best (i.e., had the highest likelihood) when we assumed that cadmium affected the third stage. Thus the risk estimates presented in the enclosed table were from a 5-stage model with cadmium exposure affecting the 3rd stage.

We hope this additional information will be useful to OSHA in the finalization of the cadmium standard. Of course, we would be happy to discuss with you further any aspects of our statistical analyses. Please feel free to call me if you have any questions (513-533-8307).

Sincerely yours,

Leslie T. Stayner, Ph.D.
Assistant Director for Risk Assessment
Division of Standards Development
and Technology Transfer

2 Enclosures

cc:
R. Lemen
R. Niemeier
L. Reed
D. Manning
T. Schnorr
K. Crump
M. Thun

NIOSH/DSDTT:LStayner:ls/dm:TaftSB-52:Cinti:OH:2/7/92:cadmium.fre

Estimates of Excess Risk per 1000 workers Based on the Poisson Regression, Cox Proportional Hazards Additive Relative Rate, and Multistage Stage Models (Lagged 5 years) Assuming 45 Years of Exposure to Cadmium and Varying the Time Weighted Average (TWA) Exposures and Continuous (CONT) Exposures.[a]

EXPOSURE		EXCESS RISK ESTIMATES (PER THOUSAND WORKERS)		
TWA[b]	CONT[c] ($\mu g/M^3$)	POISSON MODEL	COX MODEL	MULTISTAGE MODEL[d]
1	0.22	1.8	0.8	1.1
3	0.66	5.4	2.3	3.3
5	1.10	9.0	3.9	5.5
7	1.53	12.5	5.4	7.7
10	2.19	17.8	7.7	11.0
20	4.38	35.1	15.3	21.8
40	8.77	68.2	30.3	42.9
50	10.96	84.1	37.7	53.2
100	21.92	157.0	73.0	102.2
200	43.84	275.7	137.6	189.1

a. Risk estimates are based on models fitted using an additive relative rate functional form.
b. The TWA multiplied by 45 years is equivalent to the cumulative exposure estimates that were used for fitting the regression models.
c. Continuous exposure estimates were estimated based on the assumption that workers in this study were exposed for approximately 8 hours per day and 240 days per year (i.e. CONT=TWA*8/24*240/365). The continuous exposure may be thought of as the equivalent for exposures occurring in the general environment, which are generally constant during the day and year.
d. The multistage model was fitted assuming 5 stages. The likelihood of this model was maximized with the 3rd stage affected by cadmium exposure and the results from this model were used for this table.

A mathematical derivation connecting the Armitage-Doll and Cox proportionate hazards models

Randall Smith, Leslie Stayner
NIOSH

This note examines the Armitage-Doll model of carcinogenesis when a single stage is affected by dose. This derivation is based on an approximation to the cumulative hazard function as given by Crump and Howe (1984). The corresponding age-specific rate is obtained and rewritten as the product of a relative rate function times a baseline rate.

Notation and Definitions

K	number of stages in the Armitage-Doll model
r	the stage which is affected by dosing
C(t)	exposure concentration at age t
D(t)	dose rate to tissue at age t
H(t)	cumulative hazard function for first tumor occurrence in the tissue at age t
h(t)	(instantaneous) hazard function = dH/dt.

The Armitage-Doll cumulative hazard function as stated in equations A6 through A11 by Crump and Howe can be represented by

$$H(t) = q_0 t^K + q_1 \int_0^t D(u)\,(t-u)^{K-r} u^{r-1} du. \qquad (1)$$

The role of the parameter q_0 is the same as in Crump and Howe (1984) and the parameter q_1 differs from the parameter q_r used by Crump and Howe by only a multiplicative constant. This difference is unimportant since models with unknown parameters that differ only by multiplicative constants yield equivalent estimates of the hazard function. It is for this reason as well that the exposure concentration C(t) can be used in place of the tissue dose D(t) in this development if these functions are proportional to each other.

When the stage that is affected by dose is not the last stage and D(t) is differentiable, Leibniz's rule for differentiating an integral can be applied to the second term of equation 1[1]. The

---

[1] Leibniz's rule is summarized by Mood et al. (1974) as follows

resulting expression for the instantaneous hazard function is

$$h(t) = \frac{dH}{dt} = q_0 K t^{K-1} + q_1 (K-r) \int_0^t D(u)\,(t-u)^{K-r-1} u^{r-1} du \qquad (2)$$

$$= q_0 K t^{K-1} \left[1 + \frac{q_1 (K-r)}{q_0 K\, t^{K-1}} \int_0^t D(u)\,(t-u)^{K-r-1} u^{r-1} du\right] \qquad (3)$$

$$= h_0(t)\ [1 + \beta X(t)]\,, \qquad (4)$$

where

$$h_0(t) = q_0 K t^{K-1} \qquad (5)$$

$$X(t) = \frac{1}{t^{K-1}} \int_0^t D(u)\,(t-u)^{K-r-1} u^{r-1} du \qquad (6)$$

$$\beta = \frac{q_1 (K-r)}{q_0 K}\,. \qquad (7)$$

Equation (4) shows that the hazard function can be expressed as the

---

$$\frac{d}{dt}\int_{g(t)}^{h(t)} f(u;t)\,du = \int_{g(t)}^{h(t)} \frac{\partial f}{\partial t}\,du + f(h(t);t)\,\frac{dh}{dt} - f(g(t);t)\,\frac{dg}{dt}$$

where the functions f,g,h are differentiable.

product of a baseline hazard $h_0(t)$ times a relative rate function $[1 + \beta X(t)]$. The covariate $X(t)$ is a time-dependent covariate which depends on K and r and the dose history prior to age t. Hence, estimation of the relative rate can be accomplished by fixing the number of stages (K) and the stage that is affected (r) and computing the values of $X(t_i)$ for members of the cohort under observation at age t_i when the i^{th} case failed[2]. The value of $X(t_i)$ can be approximated numerically and the estimation of β can be carried out with software for fitting Cox models that accept both time dependent covariates and a relative rate function of the form $[1 + \beta X(t)]$.

---

[2] These members are often referred to as the i^{th} risk set.

References

Crump KS, RB Howe (1984). "The multistage model with a time-dependent dose pattern: applications to carcinogenic risk assessment," Risk Analysis 4(3):163-176.

Mazumdar et al. (1989). Multistage modeling of lung cancer mortality among arsenic-exposed copper-smelter workers. Risk Analysis, Vol. 9(4): 551-563.

Mood AM, FA Graybill, DC Boes (1974). Introduction to the Theory of Statistics, 3rd Edition. McGraw-Hill. New York.

Whittemore AS, JB Keller (1978). "Quantitative theories of carcinogenesis," SIAM Review 20:1-30.

END

08-29-95