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A METHOD FOR ESTIMATING THE MAGNITUDE AND TIMING OF EXCESS CANCER RISKS FROM LESS-THAN-LIFETIME EXPOSURES TO CONTAMINATED WELL WATER

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Summary

When industries improperly dispose of wastes containing carcinogenic chemicals, they can contaminate groundwater. Persons who drink this contaminated water may experience an excess risk of cancer. This paper presents an estimation method, based on the multistage model for carcinogenesis, designed to estimate the magnitude and timing of the excess cancer risks that might result from drinking groundwater contaminated by 20 years of improper disposal of industrial wastes. The proposed method generates upper bound estimates of risk that are dependent on the age distribution of the population exposed, the taste-odor threshold of the chemical in the well water, and the duration of the contamination episode. Estimates of excess cancer cases or deaths are obtained for each decade since onset of exposure for less-than-lifetime exposures for the total exposed population.

To illustrate the use of the estimation method, the present author estimates the excess cancer cases or deaths attributable to exposure to groundwater contaminated with acrylonitrile, one of the many carcinogenic chemicals currently found in industrial wastes. The excess cancer cases or deaths are shown to occur mostly between 30 and 90 years after onset of exposure under the assumption that acrylonitrile increases the transition rate for the first stage of a multistage carcinogenic process. The estimated individual lifetime excess risks range from 0.9 to 1.0%. Using estimates of excess cancer risks, decisionmakers can measure the benefits of regulations designed to control the disposal of industrial wastes.

1. Introduction

In an effort to avoid excess cancer risks in persons drinking water from groundwater sources contaminated by industrial wastes, the U.S. Environmental Protection Agency (EPA) has proposed regulations to limit improper disposal of industrial wastes that contain carcinogenic chemicals [1]. In order for the EPA or private industry to determine, for any given waste stream, the most cost-effective risk management alternative, they need realistic estimates of the magnitude and timing of the excess cancer risks that might be expected

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with each alternative management option. This paper presents a method for obtaining such estimates.

Many industrial wastes are currently disposed of in unregulated landfills. These landfills have an average useful life of 20 years. During this time and often for many years (up to 200 years) post-closure, chemicals in the wastes may leach into the aquifer below the landfill and be transported away from the landfill site. The same aquifers may serve as a source of drinking water for persons living within a few miles of the landfill site. If the concentrations of the toxic chemicals in the water are below their taste–odor threshold, people are likely to suffer prolonged exposure to the chemicals by drinking this water. If the toxic chemicals are present in concentrations above their taste–odor threshold, people are likely to suspect the contamination and, hence, cease drinking the water.

The estimation model presented in this paper is based on the multistage model of carcinogenesis [2] and generates estimates of an upper bound of the excess cancer risk for each decade after onset of exposure for persons drinking contaminated well water following a specified number of years of improper waste disposal. In the model the number and timing of the estimated cancer cases vary according to the age distribution of the population exposed, the concentration of the toxic chemical in the well water, and the duration of the contamination episode. The present author demonstrates use of the estimation model by estimating excess cancer incidence for one of the many carcinogenic chemicals currently found in industrial wastes, which, if improperly disposed, may subsequently contaminate groundwater.

This estimation model has several advantages over commonly used estimation models that assume lifetime exposures that are constant since birth for the whole exposed population and generate estimates of lifetime excess risks of cancer. First, this model estimates the impacts of less-than-lifetime exposures to hazardous substances. Second, it estimates the impact of exposure periods occurring at different ages. Third, it generates estimates of the time since onset of exposure of the excess cancer cases, and fourth it generates estimates of the average age of the victims of these excess cancers. Thus, the cancer risk estimation model described in this paper can be used to generate useful inputs for risk management decisions where it may be necessary to compare the costs and benefits of alternative disposal methods over different planning horizons.

2. Cancer risk estimation model

Based on the results of animal experiments, the EPA Carcinogen Assessment Group (CAG) has computed risk-specific doses (RSDs) for many chemical carcinogens using a linearized multistage model [3]. For this model, the RSD, as computed by CAG, is the 95 percent upper confidence limit estimate

of the dose at which a lifetime of exposure would result in one extra case of cancer for every 100,000 individuals so exposed. The carcinogen is assumed to increase the risk of a currently occurring cancer in exposed individuals.

Using CAG's value for the RSD, and making assumptions about the number of stages in the carcinogenic process and the stage(s) affected by the carcinogen, the multistage model can be manipulated to give estimates of age-specific excess cancer incidence rates for any actual dose pattern and age at first exposure [4–6]. The model assumes that cancer is a multistage process with k stages that the cell must go through before it is cancerous but that only the r^{th} stage is influenced by the toxic chemical, and that the mean time to clinical appearance of the cancer after all stages are completed is 0 years. If the individual is exposed from birth on to a constant daily dose, d, of the toxic chemical, the transition rate from the affected stage to the next stage is assumed to be

$$\lambda_r' = \lambda_r + \beta_r d, \tag{1}$$

where λ_r is the spontaneous transition rate to the next stage and $\beta_r d$ is the increase in transition rate attributable to the exposure [2]. For low transition rates, $I(t)$, the clinical cancer incidence rate in the absence of exposure in an organ containing N cells, at time t for a k stage process is approximately as follows [7]:

$$I(t) \approx N \cdot \lambda_0 \cdot \lambda_1 \ldots\ldots \lambda_{k-1} \frac{(t)^{k-1}}{(k-1)!}. \tag{2}$$

When the rth stage is affected by the toxic chemical, from eqns. (1) and (2), the incidence rate at time t with lifetime exposure to the chemical is:

$$\begin{aligned} I'(t) &\approx N \cdot \lambda_0 \cdot \lambda_1 \ldots (\lambda_r + \beta_r d) \ldots \lambda_{k-1} \frac{t^{t-1}}{(k-1)!} \\ &\approx I(t) + \frac{\beta_r}{\lambda_r} \cdot d \cdot I(t) \end{aligned} \tag{3}$$

The *excess* incidence rate for each age, $EI(t)$, is therefore:

$$EI(t) \approx \frac{\beta_r}{\lambda_r} d \cdot I(t) \tag{4}$$

where $I(t)$ is the baseline age-specific incidence rate for all cancers and d is the dose of the toxic chemical in mg/kg day. The cumulative excess incidence at the end of life can thus be approximated by:

$$\sum_{t=0}^{T} P_A(t) \cdot \gamma \cdot d \cdot I(t) \tag{5}$$

where

T = the maximum life span,
0 = the mean time to clinical appearance after all stages are completed,
$P_A(t)$ = the probability of being alive at time t,
γ = β_r/λ_r,
d = the dose in mg/kg day, and
$I(t)$ = the annual baseline cancer incidence rate at time t.

In order to derive a working approximation for the constant $\beta_r/\lambda_r=\gamma$ we use the CAG value for the RSD for the toxic chemical of interest – the dose at which a lifetime of exposure would result in one extra case of cancer for every 100,000 exposed individuals. The RSD is generally estimated by using cumulative incidence data from animal experiments where approximately lifetime exposure to the chemical at a constant level is the rule. If d in eqn. (5) is CAG's computed dose at which the estimated cumulative excess incidence is 10^{-5}, the RSD, a value for the constant $\beta_r/\lambda_r=\gamma$, can be approximated quite simply by solving the following equation for γ:

$$\sum_{t=0}^{T} P_A(t)\cdot\gamma(\mathrm{RSD})\cdot I(t)=10^{-5} \tag{6}$$

Where exposure to the toxic chemical is for less than a lifetime and follows a step function, by using the results presented in the appendix in Crump and Howe [2], the excess incidence rate at time t is given as follows:

$$EI(t)=\frac{\gamma\cdot\dfrac{dZ_{rk}(t)}{\mathrm{dt}}}{kt^{k-1}}\cdot I(t) \tag{7}$$

where Z_{rk} is a function of k, the number of stages, and r, the stage affected by the carcinogen, as well as the level and duration of exposure to the chemical. For a given r and k, it is quite easy to compute $Z_{rk}(t)$ from the form given for it in Crump and Howe [2] for dose patterns that follow a step function, that is, exposure at level d_1 for the first S years of life, then exposure at level d_2 for the next S–SS years of life and a level d_3 for the remaining lifetime. For example, if only the first stage ($r=1$) is affected by the carcinogen and the exposure level is:

$$d=d(t)=d_1=0 \text{ for } 0\le t\le S$$
$$=d_2 \quad \text{for } S<t\le SS$$
$$=d_3=0 \text{ for } t>SS$$

then

$$EI(t)=0 \quad \text{for } t\le S$$

$$EI(t) = \gamma \cdot d_2 \frac{(t-S)^{k-1}}{t^{k-1}} \cdot I(t) \quad \text{for } S < t \leq SS \tag{8}$$

$$EI(t) = \gamma \cdot d_2 \frac{[(t-S)^{k-1} - (t-SS)^{k-1}]}{t^{k-1}} \cdot I(t) \quad \text{for } t > SS$$

To convert the excess incidence of all cancers at each age into lifetime excess risks, a nonstationary Markov process is modelled [8] that assumes that the individual is in one of four alternative states during each year of the rest of their life after exposure onset. These four states are:

1. Alive, no excess cancer attributable to the specific chemical exposure;
2. Alive, cured of excess cancer attributable to the specific chemical exposure;
3. Dead of an excess cancer attributable to the specific chemical exposure; and
4. Dead of all other causes.

At the start of exposure, an individual has a probability 1 of being in state 1, and at age 90, a probability 1 of being in states 3 or 4, i.e., dead, is assumed. An individual is assumed to be able to contract only one excess cancer attributable to exposure to the specific chemical in a lifetime. If the chemical-related cancer is fatal, the patient is assumed to die in the year it is detected. The transition matrix for each year is estimated and used to derive estimates of the probability of an individual's entering any of the states [5].

The transition matrix can be written as:

$$\begin{bmatrix} P_{11} & P_{12} & P_{13} & P_{14} \\ 0 & P_{22} & 0 & P_{24} \\ 0 & 0 & P_{33} & 0 \\ 0 & 0 & 0 & P_{44} \end{bmatrix}$$

The transition probabilities are derived as follows:

$P_{11} = 1 - [EI(t) + MR(t)]$, $P_{22} = 1 - MR(t)$,
$P_{12} = EI(t) \times CR$, $P_{24} = MR(t)$,
$P_{13} = EI(t) \times (1 - CR)$, $P_{33} = 1$, and
$P_{14} = MR(t)$, $P_{44} = 1$

where

$EI(t)$ = annual excess incidence of cancer from exposure to toxic chemical estimated from eqn. (8) at the beginning of each year,
$MR(t)$ = annual death probability from all other causes including background cancers, and
CR = cure rate for cancer from chemical exposure.

The health effects of exposure to the toxic chemical are estimated separately

for 10-year age cohorts. The lifetable model is extended to allow for a new cohort of exposed individuals to be added each decade, at a mean age of 5 years and equal in size to the youngest cohort in the original population, to allow estimation of the excess cancers in those born after the start of contamination. For an individual from each age group, for each year starting from the year of first exposure and continuing until age 90, the appropriate transition matrix is estimated and used to multiply the initial state vector to give a new state vector. The probability of the individual dying of excess cancer (entering state 3) during each year is multiplied by the number of people in the age group to obtain an estimate of the number of excess cancer cases each year after onset of exposure. Estimates of cancer cases each year are derived from the estimates of deaths using the cure rates [cases = deaths/(1 − cure rate)]. The results for all age groups are then aggregated to give, for each decade after onset of exposure, the expected number of cancer cases attributable to chemical exposure.

The exposed population is assumed to follow the U.S. population in terms of sex, race, smoking habits, and age distribution [9]. The 1978 U.S. life tables are used to estimate age-specific death probabilities from all causes. Baseline incidence rates for all the cancers thought to be related to chemical exposure are taken from the Surveillance, Epidemiology and End Results (SEER) study [10]. The cure rates for cancers of interest are estimated using data from Axtell et al. [11].

3. Waste stream modeled

Acrylonitrile, CAS No. 107-13-1, is a nitrile of acrylic acid. It occurs in the waste streams generated during the production of acrylamide (SIC 2869). These are currently unregulated. To illustrate the use of the proposed estimation model, the present author estimates the cancer risks attributable to acrylonitrile in the wastes from two plants that produce acrylamide using acrylonitrile and sulfuric acid. The annual volume of waste has been estimated to be 11,000 metric tons per plant with a concentration of acrylonitrile of 5,000 ppm [12]. There is both human and animal evidence for carcinogenicity, and CAG has derived an RSD for humans of 4.3×10^{-5} mg/kg day using data from animal studies.

Table 1 presents the assumed or estimated values of all parameters used as inputs in the cancer risk estimation model described above. The estimated well concentration and duration of exposure depend on the solubility, mobility (the ability of a chemical once in solution to move through soil or rock), and persistence (the tendency of a chemical to be changed due to biological degradation or chemical reactions with other substances in the environment) of the chemical. Well concentration estimates also depend on the concentration of the chemical in the waste stream and climatic and geologic factors. A previous study estimated the average concentration of acrylonitrile in the well water as 6.23 mg/L following disposal of 11,000 metric tons of waste (5,000 ppm acryl-

TABLE 1

Input parameters for cancer risk estimation model for acrylonitrile[a]

Input parameter	Value used
Type of cancer	unspecified
Cure rate	0.386
Risk Specific Dose	0.00004 mg/kg day
No. of people exposed	2,000/plant
Well concentration	6.23 mg/L
d_2 = dose in mg/kg day (for 70 kg person drinking 2L/day of well water)	0.178 mg/kg day
Duration of exposure from 20 years' disposal	20 years
Taste-odor threshold	18.6 mg/L

[a]Source: Research Triangle Institute, Regulatory Impact Analysis for Expansion of Toxicity Characteristic Under RCRA, report prepared for Office of Solid Waste, U.S. EPA, Contract No. 68-01-7075 (October 1985).

onitrile) in an unlined landfill [12]. Moreover, acrylonitrile is assigned a low persistency rating based on its log (octanol/water) coefficient of 0.92, and therefore leaching into the aquifer is assumed to occur during the period of disposal only (20 years). (See Reference 12 for a complete description of the derivation of these parameter values.) The well concentration of acrylonitrile is estimated to be below its taste-odor threshold of 18.6 mg/L, and thus detection is unlikely and prolonged exposure to the contaminated water is to be expected.

The number of people drinking the water from each aquifer is assumed to be 2,000 for each year of contamination. This number is based on the assumption that a community well, located 1,300 meters from the landfill, draws water from the aquifer, and has an average capacity sufficient for 5,700 people, but operates at less than full capacity [13]. If only residential wells were located near the landfill, an exposed population of 200 should be assumed [14]. The estimated cancer cases resulting from such exposures are presented in the section below.

5. Results

Table 2 presents estimates of the number and timing of expected cancer cases after onset of exposure, attributable to 20 years of disposal of the hazardous waste containing acrylonitrile from a single plant in an unregulated landfill. In all cases, acrylonitrile is assumed to affect the first transition of a multistage carcinogenic process. The total number of cases predicted using the

4-stage model is 26.4, with most occurring 30 to 90 years after the beginning of exposure to the waste. Using the 7-stage model, the present author predicts 24.1 excess cancer cases with most occurring 40 to 100 years after the beginning of exposure to the waste. The mean age of those contracting cancer is 66.7 years for the 4-stage model and 66.5 years for the 7-stage model. The number of plants is estimated to be 2 for acrylonitrile [12]. Thus the total projected number of excess cancer cases from 20 years' disposal of the wastes is 52.8 (4-stage model) or 48.2 (7-stage model) in a total exposed population of approximately 5,168. The exposed population includes 4,000 persons exposed from the onset of well contamination and two cohorts of 584 children each, born during the contamination episode. The individual lifetime excess risks among those exposed to the contamination episode are thus projected to be 1.0×10^{-2} (4-stage) or 0.9×10^{-2} (7-stage), a very significant risk indeed.

The main difference observed between the results from the 4- and 7-stage models is the difference in time since onset of exposure. The excess cancer cases for the 7-stage model are estimated to occur approximately 10 years later than those for the 4-stage. The number of cases and the mean age of the victims are very similar for both models. If, instead of an unspecified cancer site, for example, only excess liver cancers had been assumed, the resulting estimates of excess cancer cases would be almost identical to those presented because of the method used to estimate γ. However, the estimated values of the constant, γ, would be very different for the two cases and the estimated number of cancer deaths would be higher.

TABLE 2

The expected cases of cancer attributable to exposure to acrylonitrile following 20 years' disposal in an unregulated landfill for 2,584 exposed persons

Years following beginning of disposal	Excess cancer cases	
	4-Stage model	7-Stage model
0- 10	0.001	0.000
10- 20	0.094	0.023
20- 30	0.630	0.180
30- 40	1.900	0.680
40- 50	3.810	1.900
50- 60	5.540	3.950
60- 70	5.990	5.800
70- 80	4.790	5.930
80- 90	2.650	3.970
90-100	0.880	1.490
100-110	0.120	0.220
All years	26.400	24.140

TABLE 3

The expected cases of cancer attributable to twenty years' exposure to acrylonitrile starting at different ages for 2,000 exposed persons

Years following beginning of disposal	Age at Onset of Exposure							
	0 years		5 years		25 years		55 years	
	4-Stage	7-Stage	4-Stage	7-Stage	4-Stage	7-Stage	4-Stage	7-Stage
0-10	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
10-20	0.10	0.10	0.14	0.04	0.07	0.00	0.08	0.00
20-30	0.52	0.52	0.65	0.32	0.71	0.06	0.36	0.01
30-40	1.20	1.30	2.00	1.30	2.70	0.42	0.20	0.01
40-50	2.60	3.10	5.70	4.20	5.40	1.30		
50-60	5.80	7.70	11.00	9.40	5.80	1.80		
60-70	10.00	14.00	16.00	14.00	1.70	0.63		
70-80	13.00	19.00	14.00	14.00				
80-90	10.00	16.00	3.00	3.60				
90-100	2.50	3.90	0.00	0.00				
100-110	0.00	0.00	0.00	0.00				
110-120	0.00	0.00	0.00	0.00				
Total	46	65	53	47	16	4	0.6	0.02
Average age	64	65	66	68	71	74	80	83
Lifetime risk	2×10^{-2}	3×10^{-2}	3×10^{-2}	2×10^{-2}	8×10^{-3}	2×10^{-3}	3×10^{-4}	1×10^{-5}
Reduction in disease-free period (years)	0.38	0.52	0.39	0.31	0.09	0.02	0.002	0.00003

Table 3 presents estimates of excess cancer cases for different age cohorts exposed to acrylonitrile for 20 years. This table illustrates the impact of age at exposure on the lifetime excess risk of cancer. For example, the lifetime excess risk is approximately an order of magnitude less when comparing the risks of exposure during childhood with the risks of exposure as a young adult. Table 3 illustrates the increase in average age of the victims as age at onset of exposure increases. Table 3 also illustrates the higher average age when using the 7-stage model compared to the 4-stage model. Finally, Table 3 illustrates the lesser impacts on the older age cohorts estimated when using the 7-stage model rather than the 4-stage model. Reductions in the disease-free period are presented in Table 3. They are computed as the average difference between exposed and non-exposed persons in the number of years alive and without cancer attributable to the acrylonitrile exposure.

6. Conclusions

The cancer risk estimation method described in this paper differs from currently used risk assessment methods that assume lifetime exposures. The impacts of less-than-lifetime exposures are estimated, as well as the timing and magnitude of the excess cancer incidence. Estimates of excess cancer cases for each time period after exposure and each age group of persons exposed are derived under the assumption that the toxic chemicals increases the incidence of a currently occurring cancer by increasing the transition rate between one of the postulated many stages a cell passes through before it becomes malignant. Exposure duration and competing causes of death are included explicitly in the estimation method.

Efficient risk-management of hazardous waste requires comparing both the costs and health effects of different management alternatives for a given duration of waste disposal. Estimated changes in both costs and health effects associated with a change in management practice can be used as inputs to risk management decisions. It is inappropriate, however, to estimate changes in the annual costs of waste management associated with a change in management practice while estimating changes in health effects associated with a lifetime of disposal (usually assumed equal to 70 years). Division by 70 of these lifetime health effects changes to obtain an annual health effect change is misleading since, after a change in management practice, it would take a long transition period, up to 70 years, to reach the new annual health effect assuming lifetime exposures. In contrast, the annual cost changes would occur without such a transition period. Thus the health effects of a change in management practice would be overestimated in the early years. In addition to this natural transition period, changing production levels may result in a constant lifetime exposure level never being reached. The estimation method proposed in the paper can be adapted to allow for changing production levels.

The estimates of the timing of the excess cancer cases must be viewed as suggestive only, since they depend on assumptions about the number of stages in the carcinogenic process and the particular stage affected by the toxic chemical. For example, the later the stage affected by the toxic chemical the shorter the time lag between exposure and disease onset. However, significant time periods between onset of exposure and cancer incidence have been frequently observed in workers exposed to carcinogens. As more is learned about the mechanisms of carcinogenesis and the specific impacts of each toxic chemical, the estimation model presented can be modified to generate more realistic estimates about the magnitude and timing of the excess cancer incidence resulting from exposure to carcinogenic chemicals. In the meantime, sensitivity analysis could be used to develop ranges of estimates with alternative assumptions.

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