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EPIDEMIOLOGICAL CRITERIA FOR OCCUPATIONAL CARCINOGEN STANDARDS

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ABSTRACT

The California Legislature, impatient with the slow process by which workers were being protected from carcinogens in the workplace, directed the California Department of Health to recommend, and to document the support available for enforceable standards for occupational carcinogens. At first, our effort was to focus on those fourteen substances already identified, plus vinyl chloride, and asbestos. We were further directed to recommend and support standards for carcinogens, for which federal regulations had not yet been established.

The first task was to identify potentially carcinogenic materials for which data on carcinogenicity existed, for which California workers were exposed, and for which a supportable standard could be developed. We then proposed three sets of questions which needed to be answered before an enforceable standard would be proposed:

1. Is the material capable of producing cancer among persons who are occupationally exposed?

2. What is known about dose-response relationships, detectability and measurability under realistic circumstances, and potential for avoidance of, or protection from exposure? What are health hazards of likely alternative materials or practices?

3. At what level is risk both socially acceptable and regulation enforceable?

We selected arsenic (As), coal tar pitch volatiles (CTPV) and aminotriazole (amitrol) for initial consideration. By the criteria we adopted a positive answer to question 1 was given for all three. Epidemiological evidence was important in dealing with all three substances.

We recommend standards at 2 $\mu g/m^3$ for a long-term average for arsenic, at 0.1 mg/m^3 for eight to ten hours for CTPV, and at 50 $\mu g/m^3$ for eight hours for amitrol.

The process of setting standards is perceived as being not solely a scientific one, although scientific evidence, scientific judgement, and scientists are involved. The process involves such value-related (that is non-scientific) questions as the alternative materials and processes available, the uniqueness of the product, the relative value of protective devices and practices compared to identifiable health risks.

Setting standards for carcinogens poses even more difficult problems because of the usually long latent period between exposure and manifestations of

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cancer, the important role of co-factors, and in light of these, the great importance of animal and *in vitro* tests (including bacterial mutagenic tests) as warning of the potential carcinogenicity of new chemicals for which an otherwise valuable use can be identified.

This report deals with the special role of epidemiological evidence and interpretations in this difficult process. It was initiated prior to the promulgation of Proposed Regulations of the U.S. Occupational Safety and Health Administration for the Identification, Classification, and Regulation of Toxic Substances Posing a Potential Occupational Carcinogenic Risk to Humans, and the extensive hearings on these (OSHA Docket No. 090).

The point of view in this paper is the author's own, but it reflects views and judgements thoroughly reviewed with colleagues in the California Department of Health Services and in occupational medicine. Some of the most contentious issues raised during the hearings on OSHA Docket No. 090 would be resolved or much simplified by the approach proposed here. Among them are the criteria for using animal experimental data for indicating the need for regulation, and the difficulties of defining acceptable thresholds for carcinogenicity.

The paper is divided into sections on: Legislative and administrative background, Choice of substances, Questions defining criteria for a standard, Data relevant to these questions, and Discussion and applicability.

LEGISLATIVE AND ADMINISTRATIVE BACKGROUND

As a result of extensive hearings on problems of occupational cancer the California Legislature passed and the Governor signed into Law SB 1678 which was directed at prevention of job-induced cancer. It required registration of employers using any one of fourteen materials previously identified by the OSHA as carcinogens, as well as vinyl chloride and asbestos, for each of which standards were to be adopted or set by the State Occupational Safety and Health Standards Board. In addition, the Health Department's Occupational Cancer Control Unit was directed to recommend to the Board standards for the materials for which Federal regulations had not yet been adopted.

Committees and working groups were established to undertake the tasks which this implied, namely selection of agents which met the requirements of the law, which involved exposures of California workers, and about which enough was known to make it likely that a good case could be presented to the Standards Board.

Since it was the Standards Board, and not the Health Department and its staff which had statutory authority to adopt standards, the task of the Department was to decide on whether a risk of cancer existed for persons occupationally exposed to these materials, and at what levels, and then to propose enforceable standards. It was the task of the Standards Board to decide if the risks were acceptable on the basis of evidence and arguments before them. Extensive discussions and input from employers and from workers were part of the procedure adopted.

CHOICE OF SUBSTANCES

From over twenty substances considered three were selected. The criteria were the numbers of California workers at risk, the strength of the evidence, and the presumed feasibility of enforcing regulations to reduce exposures. The materials selected were arsenic (As), coal tar pitch volatiles (CTPV) and aminotriazole (amitrol). Arsenic exposures were mostly in primary smelting and metal refining, secondary smelting, and the production and use of agricultural chemicals. CTPV exposures were in coking ovens, blacksmith and other metal treatment. Exposures to amitrol occurred among highway, utility, and mosquito abatement district staffs who used the material as a weed killer. (It was banned from use on food crops since 1959 because it had been shown to induce thyroid tumors in rats.)

QUESTIONS DEFINING CRITERIA FOR A STANDARD

1. Is the material capable of producing cancer among persons who are occupationally exposed?

An affirmative answer to this question defines the need for a standard. The question in contrast to the usual introductory question asks for more information and judgement than the more usual question: "Is the material capable of causing tumors in experimental animals (or man) by any route or at any dose?"

The answer to the question we pose is not the natural result of any one single experiment or a single epidemiological study. We thus had to decide by what principle the question was to be answered.

Since the purpose of the standard-setting effort was regulatory rather than advancement of knowledge, we decided that legal guidelines for relative certainty, rather than scientific ones should be used. For the most commonly used scientific guideline "statistically significant" there exists a crudely parallel legal guideline "beyond a reasonable doubt", customarily applied in criminal cases. This guideline we felt to be too demanding to provide a satisfactory level of health protection from such a risk as cancer. We therefore chose the guideline, "by a preponderance of evidence", the usual criterion in administrative law, which in most circumstances will be the type of practice which determines the legal soundness of a standard.

Despite the many pages of scientific opinion on such issues which have been before the Environmental Protection Agency[5] as well as before the Occupational Health and Safety Administration, the decision must be judged by legal rather than scientific criteria; the legal criteria, however must be informed by scientific evidence, the certainty of which can usefully be assessed by scientists. A decision as to whether a given agent under defined conditions produces tumors in experimental animals, or has produced excess cancer in humans is a scientific decision, but a decision as to whether a tumor-causing agent in experimental animals will or will not produce cancer in occupationally exposed workmen, with sufficient certainty to justify or preclude its regulation is not solely a scientific question. It is a legal question to which scientific evidence addresses itself.

We also adopted the view that evidence on human reactions and even ambiguous epidemiological evidence of human carcinogenesis had greater weight in the preponderance of evidence than did animal experiments, however unambiguous.

2. What is known about dose-response relationships, detectability and measurability under realistic circumstances, and the potential for avoidance of, or protection from exposure? What are the health hazards of likely alternative materials or practices?

This set of questions is analogous to requiring the preparation of a criteria document, and has been treated in this way. That process is sufficiently well known so as to require little comment. However, we did make one policy decision which deserves comment. We decided following the National Academy of Science Report[10] that: "Methods do not now exist to establish a threshold for long-term effects of toxic agents". This discarding of threshold assumptions for carcinogens has long been accepted in radiation carcinogenesis.

Dr Arthur Upton, Director of the National Cancer Institute restated these principles in his testimony on the OHSA Docket No. 090[16]:

A. Any exposure to ionizing radiation is considered to pose some risk of increased cancer incidence.

B. At low exposures, the excess risk is considered likely to be proportional to the increase in exposure (relative to background).

C. Permissible exposures to radiation are to be set as low as readily achievable (reflecting a judgement that no increase in radiation exposure that is unnecessary or does not involve a benefit is socially acceptable).

As long as some dose-response data for chemical carcinogens are available from human studies, it is possible to discuss how much lower exposures can be to reach a level which is both detectable and socially acceptable in light of the potential or assumed benefit. This approach simply does not require establishment of a threshold.

While for a given short term experiment it may be possible to define a concentration and duration above which certain acute effects just begin to occur with significant frequency, this approach simply cannot be applied to long-term effects, and can only be of limited value in human studies. It is not a meaningful approach to interpretations of epidemiological evidence. Thus the avoidance of threshold assumptions is characteristic of the epidemiological approach to standard setting.

If a material can be considered a human occupational carcinogen, from a scientific or medical point of view, the only "allowable concentration" or "acceptable level" is the lowest one attainable, and preferably zero. However, there are two constraints in the situation which keep us from applying this no--exposure approach. First is that we have already defined the process as predominantly social or legal, rather than scientific or medical, so what we seek is a socially acceptable level. If the standard is to be enforceable we need to be able to determine if it is exceeded or not. We must be able to measure the material against the usual background and state whether exposure conditions are or are not within the levels established as "socially acceptable". The decisions as to levels which have social acceptability will be those arrived at by the Standards Board. These considerations lead to the third question.

3. At what level is risk of cancer both socially acceptable and the regulation enforceable?

DATA RELEVANT TO THESE QUESTIONS

There is a special importance of epidemiological data relevant to these questions. Animal experiments which are said to show that a material is carcinogenic, must, in the author's personal view, by a route and dose likely to be realistic for human exposure before they approach the point that a preponderance of evidence indicates the material may be carcinogenic for man. If human exposures could have occurred, (that is the material is already in use) and the time elapsed sufficient (decades) for the possibility of human carcinogenesis, then positive epidemiological evidence of even suggestive and inconclusive sort will suffice along with animal results to decide question 1 positively. If in addition to positive animal data, human exposures show substantial uptake, retention, or other physiological or biochemical criteria of impairment, even in the absence of sufficient time to develop cancer, this suffices to establish in my view, a preponderance of evidence. The strength is greater, if physico-chemical similarity to known human carcinogens can be shown. It must be clear that different observers will weight different items of evidence differently.

Arsenic

Inorganic arsenic is capable of producing cancer among occupationally exposed workers, beyond a reasonable doubt

An authoritative review by the National Academy of Sciences[12] concludes: "There is strong epidemiological evidence that inorganic arsenic is a skin and lung carcinogen in man. Skin cancer has occurred in association with exposure to inorganic arsenic compounds in a variety of populations including patients treated with Fowler's solution, Taiwanese exposed to arsenic in artesian well water, workers engaged in manufacturing of pesticides and vintners using arsenic as a pesticide. Lung cancer has been observed to be associated with inhalation exposure to arsenic in copper smelters, workers in pesticide manufacturing plants, Moselle vintners and Rhodesian gold miners. Two of the three smelter studies showed a gradient in the incidence of lung cancer with the degree of arsenic exposure; one of these studies also suggested that sulfur dioxide may be a carcinogenic co-factor for the lung." Smoking histories were not evaluated in these earlier smelter studies. Rencher's and his co-workers'[15] examination of mortality data in Utah copper smelter workers, including smoking information, supports the previous findings of excessive lung cancers.

Coal tar pitch volatiles

Coal tar pitch volatiles are capable of producing cancer among occupationally exposed workers beyond a reasonable doubt. It is now 202 years since Percival Pott[13] first connected the occurrence of scrotal cancer to the occupation of being a chimney sweep, and over 100 years ago Manouvriez[8] showed coal tar to be a skin carcinogen for animals. Forty years have passed since the first epidemiological study showed excess lung cancer among steel workers[6].

The evidence has piled up since that skin and respiratory cancer rates are increased in coal tar pitch exposed workers, who can have increased folliculitis of skin and photosensitization as well as increased frequency of bronchitis. Increased rates for bladder cancer, kidney cancer, and leukemia have been reported by some workers[3].

Among the workers affected are coke oven workers, gas retort workers, roofers, welders of pitch lined pipes, chemical plant workers, and fishermen who mend coal-tar soaked nets using the mouth to act as a "third hand", which causes lip cancer.

Papillomata and pigmentary changes in the skin often precede skin cancer.

The coke oven workers who work longest on top of ovens have greater cancer hazards than workers on part-time "topside" or "side oven" workers [7,14].

Aminotriazole

Aminotriazole is capable of producing cancer in occupationally exposed workers, by a preponderance of evidence. That aminotriazole was an animal carcinogen was known since 1959, when cranberries and cranberry products were taken off the U S market because residues of amitrole were found on them. Cancellation of registered use on crops followed in a few years. The basis was the production of thyroid tumors in rats, fed orally.

The International Agency for Research on Cancer (IARC) in reviewing the evidence for carcinogenic risk for a number of substances[4] concludes that animal data showed that amitrole induced thyroid and liver tumors in both mice and rats following oral and/or subcutaneous administration.

Axelson and Sundell[1] reported a cohort study of Swedish railway workers exposed to a variety of herbicides. Within the group exposed to aminotriazole alone or in combination, 7 cancers were observed compared to 1.9 expected. Continued follow-up reveals that the trend toward excess is increasing.

The IARC appraisal in 1974[4] concluded that a single, small, cohort study raises the suspicion that amitrol may be carcinogenic to man, but the findings cannot be regarded as conclusive. Hence we conclude that the findings are not beyond a reasonable doubt, but are convincing by a preponderance of evidence. In other words, it is more likely than not that amitrole is an occupational carcinogen.

Dose-response data

Dose-response information for arsenic exposures was review on the basis of Ott's and co-workers' report[12] and in light of the case study approach proposed by Blejer and Wagner[2]. This led us to propose a standard at 2 $\mu g/m^3$ for a long term average.

The paper by Mazumdar and co-workers[9] on coke oven workers in the steel industry provided some dose-response data, from which, along with evidence of detectability led us to propose a standard for CTPV of 0.1 mg/m^3 for eight to ten hours.

The Axelson and Sundell study[1] did not provide much dose-response information, but the criteria of laboratory detectability led us to a tentative standard of 50 μg/m^3 for eight hours for aminotriazole. Measurements of exposure to similar materials under conditions of similar spraying practices and further laboratory results may require changes in this standard.

DISCUSSION AND APPLICABILITY

Subsequent to our work, the US Department of Labor, OSHA published its "Final Standard" for Arsenic (Federal Register May 5, 1978). It is 10 μg/m^3 for 8 hours which will "provide significant employee protection and is the lowest feasible level in many circumstances". The difference from our recommendation is less than it appears as we recommend a "long term average". If an eight hour standard is met routinely, the long term average may, through change of job and vacations be substantially lower. In any event feasibility of reaching a lower exposure may be better in California, now without a primary non-ferrous metal smelting industry, than in other places.

We have not yet completed the work required under SB 1678. We believe that two innovative approaches have been developed, the use of "the preponderance of evidence" criterion for deciding which materials need regulation as occupational carcinogens and the replacement of the threshold concept by criteria of socially acceptable risk at or above detectable concentrations.

REFERENCES

1. *Axelson, O. and Sundell, L.* Herbicide exposure mortality and tumor incidence. An epidemiological investigation on Swedish railroad workers. Work-Environ. Health, **11** (1974) 21–28.
2. *Blejer, H. P. and Wagner, W.* Inorganic Arsenic – Ambient Level Approach to the Control of Occupational Cancerigenic Exposures. Proc. N.Y. Acad. Sci., **271** (1976) 179–186.
3. *Doll, R., Vessey, M. D., Beasley, R. W.* Mortality of gasworkers: Final Report of a Prospective Study. Br. J. Ind. Med., **29** (1972) 394–406.
4. *International Agency for Research on Cancer.* IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Vol. 7, Lyon, IARC, 1974.
5. *Karch, N.* Explicit Criteria and Principles for Identifiying Carcinogens: A Focus of Controversy at the Environmental Protection Agency and Mc Cray L. Mouse Livers, Cutworms, and Public Policy: EPA Decision Making for the Pesticides Aldrin and Dieldrin. In Vol. II a Decision Making in the Environmental Protection Agency: Case Studies Commission on Natural Resources of the National Academy of Sciences, 1977, Washington.
6. *Kuroda, S. and Kawahata, K.* Uber die gewerbliche Entschtelung des Lungenkrebses bei Generatorgassarbeitern. Z. Krebsforsch., **45** (1937) 36–46.
7. *Lloyd, J. W.* Long-Term Mortality Study of Steel Workers. V Respiratory Cancer in Coke plant Workers. J. Occup. Med., **13** (1971) 53–68.

8. *Manouvriez, A.* Maladies et hygiene des ouvriers, travaillant a la fabrication des agglomérés de houille et de brai. Ann. Hyg. Publ. (Paris), **45** (1876) 459–464.

9. *Mazumdar, S., Redmond, C., Sollecit, W., and Sussman, M.* Epidemiological Study of Exposures to Coal Tar Pitch Volatiles Among Coke Oven Workers. J. Air Pollut. Control Assoc., **25** (1975) 382–389.

10. *National Academy of Sciences.* National Research Council – Drinking Water and Health, 1977, Washington.

11. *National Academy of Sciences,* National Research Council, Medical and Biological Effects of Environmental Pollutants-Arsenic, Washington, 1977.

12. *Ott, M. G., Holder, B. B., Gordon, H. L.* Respiratory Cancer and Occupational Exposure to Arsenicals. Arch. Environ. Health, **29** (1974) 250–255.

13. *Pott, P.* Cancer Scroti. In: Chirurgical Observations: 63–68, Hawes, Clarke, and Collins, London, 1775 (quoted from Wagoner J. K. Proc. N.Y. Acad. Sci., **271** (1976) 1–4).

14. *Redmond, C. K., Ciocco, A., Lloyd, J. W.* Longterm Mortality Studies of Steelworkers VI. Mortality from Malignant Neoplasms among Coke Oven Workers. J. Occup. Med., **14** (1972) 621–629.

15. *Rencher, A. C., Carter, M. W., McKee, D. W.* A Retrospective Epidemiological Study of Mortality at a Large Western Copper Smelter. J. Occup. Med., **19** (1977) 754–758.