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The Comparative Potency Method: An Approach to Quantitative Cancer Risk Assessment

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ABSTRACT

The comparative potency method involves estimating the human carcinogenic potency of chemical agents or mixtures for which there are no human data by comparison with agents for which there are human carcinogenic data, using short-term bioassays. The method is illustrated for diesel engine particulate exhaust emissions, the heavy organics emitted from a synthetic fuel plant using solvent refined coal and for the promoting action of the pesticide DDT. A survey of human carcinogens having quantitative dose–response data is presented which indicates that the comparative potency method might be applied to liver, bladder and lung carcinogens and possibly to leukaemogens.

If one is obliged to estimate the cancer risk from a carcinogen for which there are no human data, and there is a carcinogen with similar chemical characteristics for which there is enough human dose–response information for a quantitative risk assessment, the relative potency of the two carcinogens by short-term *in vitro* and *in vivo* bioassays would permit a risk assessment to be done for the agent for which there are no human data on the basis of the agent for which there are such data. This approach was taken over twenty years ago in the case of some bone-seeking radionuclides: data were available on bone cancer induction in humans by radium-226. In order to estimate the carcinogenic effects of other radionuclides their comparative potencies relative to radium-226 were determined in dogs (Dougherty *et al.*, 1962).

In this context the approach first came up in connection with the need for a quantitative risk assessment for diesel engine particulate exhaust emissions. In 1979, when the mutagenicity of diesel exhaust was first demonstrated, there was a request to the EPA's Carcinogen Assessment Group to estimate the cancer risks of diesel engine exhausts on the assumption that a substantial proportion of the automobile fleet would be equipped with diesel engines because of the rising cost of gasoline. Since there were virtually no animal data and no epidemiological

data on the cancer risk associated with diesel engine exhaust, the only possible approach that could produce results in a relatively short period of time was to base the human lung cancer risk estimate due to diesel emissions on the lung cancer data obtained from humans exposed to other organic combustion and pyrolysis products, using *in vivo* and *in vitro* short-term bioassays to obtain the relative potencies of diesel particulates and other organic combustion and pyrolysis products. Epidemiological studies had shown an increased incidence of lung cancer in humans exposed to coke-oven emissions, roofing tar emissions and cigarette smoking. These are the only materials with some chemical resemblance to diesel particulates for which there are human cancer data. The estimation of cancer risk of diesel exhaust was therefore determined by comparing the carcinogenic potencies of diesel exhaust particulate extracts with those of coke-oven emissions, roofing tar, aerosols and cigarette smoke tars in a battery of tests including *in vitro* mutagenicity assays and mouse skin tumour initiation studies. Details of the methods and results have been presented elsewhere (Albert *et al.*, 1983). Harris has also analysed this data (Harris, 1981). The *in vitro* tests included:

(1) reverse mutation in *Salmonella typhimurium* TA 98 (Ames test),
(2) forward mutation at the thymidine kinase locus in L5178Y mouse lymphoma cells (mouse lymphoma assay) and
(3) sister-chromatid exchange in Chinese hamster ovary cells (SCE assay).

The *in vivo* test consisted of the skin initiation bioassay in the Sencar mouse. The *in vitro* and *in vivo* bioassays were done using dichloromethane extracts of the diesel and gasoline particulate samples as well as the coke-oven and roofing tar particulates; the cigarette smoke condensate was dissolved in acetone. The comparative potencies were expressed in terms of linear slopes. The human lung cancer responses to coke-oven and roofing tar emissions and cigarette smoke were expressed in terms of 'unit risk'. The unit cancer risk is predicated on the basis of a linear non-threshold extrapolation model; it is the individual lifetime excess of lung cancer risk from continuous exposure per microgram carcinogen per cubic metre of inhaled air. The average individual risk is obtained by multiplying the 'unit risk' by the average exposure; the excess number of cancer cases in an exposed population is obtained by multiplying the average individual risk by the number of people exposed. Multiplying the relative potency of the engine exhaust particulates in relation to comparative samples, for example, coke-oven emission particulates, with the 'unit risk' for coke oven would yield the 'unit risk' for engine exhaust particulates.

Table 1 shows the relative potencies of the emission extract in the various bioassay systems normalized to the coke-oven sample. It can be seen that there is a remarkable degree of correspondence between the relative potencies of the coke-oven, roofing tar and cigarette smoke condensate samples obtained from the human epidemiology data and mouse skin tumour initiation data. The

Table 1 Comparison of relative potencies of emission extracts in several bioassay systems

Sample	Human lung cancer	Mouse skin tumour initiation[a]	Mutation in L5178Y mouse lymphoma cells[b]	Mutation in Ames TA98[b] (+MA)
Coke oven	1.0	1.0	1.0	1.0
Roofing tar	0.39	0.20	1.4	0.78
CSC	0.0017	0.0011	0.066	0.52
Nissan diesel		0.28	0.24	12

[a] From papilloma multiplicity data (papillomas/mouse at 1 mg).
[b] With metabolic activation.

correspondence between the *in vitro* bioassay and the human epidemiology data for relative potencies is fairly good for the coke-oven and roofing tar samples but is poor for the cigarette smoke condensate; the Ames test gives very high values for the Nissan diesel sample in comparison to the mouse skin tumour initiation results presumably because of the responsiveness to the nitroaromatics in engine exhausts. Table 2 shows the relative potencies of the diesel and gasoline samples normalized to the Nissan sample using the mouse skin tumour initiation and the two *in vitro* bioassays with and without metabolic activation (MA). It can be seen from Table 2 that there is a fairly good correspondence between the various methods for determining the relative potencies regardless of whether MA was used, but it is somewhat better with MA.

The 'unit risk' estimate (lifetime risk/microgram organics per cubic metre) was

Table 2 Comparison of relative potencies of diesel and gasoline emission extracts in several bioassay systems

Sample	Mouse skin tumour initiation[a]	Mutation in L5178Y mouse lymphoma cells (−MA)	Mutation in L5178Y mouse lymphoma cells (+MA)	Mutation in Ames TA98 (−MA)	Mutation in Ames TA98 (+MA)
Diesel samples					
Nissan	1.0	1.0	1.0	1.0	1.0
Volkswagen Rabbit	0.41	0.23	0.25	0.34	0.23
Oldsmobile	0.53	0.29	0.45	0.19	0.11
Caterpillar	Neg	0.60	0.022	0.034	0.023
Gasoline-catalyst sample					
Mustang II	0.29	0.90	0.38	0.26	0.26

[a] From papilloma multiplicity data.

determined for the Nissan sample based on the coke-oven, roofing tar and cigarette smoke condensate samples using only the skin initiation data; the 'unit risk' averaged 3.9×10^{-4} with a range of 2.6×10^{-4} to 5.2×10^{-4}. The 'unit risk' for the other engine emission samples was based on the 'unit risk' for the Nissan sample using the comparative potency of the various engine particulate emission samples with respect to the Nissan sample based on the *in vitro* assays.

This was done because the skin initiation response was weak for all emission samples other than the Nissan, whereas the good dose–response data for all the engine samples was obtained with the *in vitro* bioassays.

Table 3 shows the unit lung cancer risk estimates for diesel and gasoline catalyst particulates in terms of the organic extracts or the whole particulates, the latter being determined from the percentage of the particles that was extractable by dichloromethane. It can be seen that the automobile diesel and gasoline engines have very similar 'unit risk' estimates ranging from 0.2×10^{-4} to 0.5×10^{-4}. The stationary caterpillar diesel showed a much lower 'unit risk'.

The comparative potency method was also used to estimate the cancer risks from heavy organics emitted from a SRC-1 (solvent refined coal) plant. The relative potency of the high boiling (> 65°F) heavy distillate fraction was determined in relation to that for benzo(a)pyrene using the skin cancer response in mice (Renne *et al.*, 1982). The potency of coke-oven particulate extracts in relation to benzo(a)pyrene was also determined by skin carcinogenesis studies in mice (Nesnow *et al.*, 1983). This enables the relative potency of the SRC-1 heavy distillate fraction to be determined in relation to coke-oven particulate extracts. In this way, the risk assessment for the SRC-1 heavy distillate fraction could be estimated from the epidemiological data on coke-oven workers. In this instance, the relative potency of the SRC heavy distillate and benzo(a)pyrene (BP) was

Table 3 Unit lung cancer risk estimates for diesel and gasoline-catalyst particulates

Emission sources	Unit-risk estimates (lifetime risk/$\mu g/m^3$) Organics	Particulates
Diesel samples		
Nissan[a]	3.9×10^{-4}	0.3×10^{-4}
Volkswagen Rabbit[b]	1.2×10^{-4}	0.22×10^{-4}
Oldsmobile[b]	1.2×10^{-4}	0.20×10^{-4}
Caterpillar[b]	$.059 \times 10^{-4}$	0.016×10^{-4}
Gasoline-catalyst sample		
Mustang II[b]	1.2×10^{-4}	0.52×10^{-4}

[a] Based on mouse skin tumour initiation.

[b] Based on the mouse lymphoma, SCE, and Ames bioassays (+MA).

determined from the temporal response data for skin cancers using the relationship dt^n = constant where d is dose and t is median time to tumour (Druckrey, 1967). The available data permitted n to be estimated as 2.9. It was found that BP was 55 times more potent than the SRC-1 process solvent and that BP was 43 times more potent than the coke-oven particulate sample extract; hence, the coke oven was 1.3 times more potent than the SRC-1 heavy distillate fraction. The 'unit risk' for coke-oven emissions as obtained from the coke-oven worker data was 9×10^{-4} per microgram per cubic metre (EPA, 1982) and the 'unit risk' for the SRC-1 high distillate fraction was estimated at 7.0×10^{-4} per microgram per cubic metre (Crump, personal communication).

The question arises as to how generally applicable is the comparative potency method for quantitative risk assessment. The method depends on having dose–response data for human cancer responses. Table 4 presents a tabulation of agents for which there is solid qualitative evidence of carcinogenicity in humans (IARC, 1979) in relation to the availability of quantitative human exposure data. It can be seen that a number of carcinogens for which there is adequate human qualitative evidence of carcinogenicity have either no or marginal exposure data.

Table 5 shows those human carcinogens which might be suitable for use in the comparative potency method. It is evident that the method might be applied to liver, bladder and lung carcinogens and possibly to leukaemogens. It is, of

Table 4 Agents for which there is sufficient qualitative evidence of carcinogenicity in humans in relation to the availability of quantitative human exposure data

Carcinogen	Target organ in humans	Quantitative exposure data in humans
4-Aminobiphenyl	Bladder	0
Aflatoxin	Liver	+
Arsenic	Lung	+
Asbestos	Lung	+
Benzene	Leukaemia	+
Benzidene	Bladder	+
Chlornaphazine	Bladder	+
BCME	Lung	−
Chromium	Lung	+
Diethylstilboestrol	Vagina	+
Ethylene oxide	Leukaemia	+
Melphalen	Leukaemia	±
Mustard gas	Lung	−
2-Naphthylamine	Bladder	+
Nickel	Nasal, Lung	±
Vinyl chloride	Liver	+
Cigarette smoke	Larynx, Lung	+
Coke-oven emissions	Lung	+
Roofing tar	Lung	+

Table 5 Human carcinogens suitable for use in the comparative potency method

Human		Test animal	
Organ	Carcinogen	Organ	Species
Liver	Aflatoxin	Liver	Rat
	Vinyl chloride	Liver	Rat, mouse
	Mestranol (promoter)	Liver	Rat
	Ethinyl estradiol (promoter)	Liver	Rat
Bladder	Benzidene	Bladder	Dog
		Liver	Rat
	Chlornaphazine	Local sarcoma	Rat
	2-Naphthylamine	Bladder	Hamster
		Liver	Mouse
Lung	Coke oven	Skin	Mouse
	Cigarette smoke	Skin	Mouse
	Roofing tar	Skin	Mouse
	Chromium	Lung	Rat
Leukaemia	Ethylene oxide	Bone marrow	Rat
	Benzene	Lymphoma	Mouse

course, necessary to have reasonable grounds for selecting the likely human target organ for carcinogens that have no human data. The situation is relatively simple with an agent like 4-aminobiphenyl. There is ample human evidence that 4-aminobiphenyl is a bladder carcinogen. However, there were no associated exposure data from which to derive a 'unit risk' estimate. Animal data, however, provide the relative potency of 4-aminobiphenyl with respect to 2-naphthylamine which does have sufficient exposure data to derive a 'unit risk' estimate.

The comparative potency method might be applicable to promoting agents. For example, mestranol has been widely used in contraceptive pills (Hatcher *et al.*, 1980). The daily mestranol-equivalent dose for such users is probably in the domain of 60 μg/day (Rooks *et al.*, 1979). The risk of hepatocellular adenomas in long-term contraceptive pill users has been estimated to be 3.5×10^{-5} per year (Rooks *et al.*, 1979). Mestranol is a promoter for liver tumours in the rat with about one thousand times greater potency than phenobarbitone (Yager and Yager, 1980); DDT is also a promoter in the rat liver with about equal potency as phenobarbitone (Peraino *et al.*, 1975). Hence, mestranol is about one thousand times more potent than DDT. As a promoter, DDT would therefore require a dose of the order of 60 mg/day to produce an annual hepatocellular adenoma risk of 3.5×10^{-5}. The relative potency of other chlorinated pesticides, herbicides and solvents which do show promoting action in the rat liver may also be similarly estimated by the comparative potency method.

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