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Detection of environmental carcinogens-DNA, par PFOHL-LESZKOWICZ, G. GUILLEMAUT, J.F. MAS-FARAUD, B. RETHER et J.M. HAGUENOER

ont fait l'objet d'intervention lors des journées scientifiques de Dijon les 31 mars et 1er avril 1995, journées organisées par l'IAI, la SFT et l'APPA.

Toxicological aspects of air pollution risk

Evaluation toxicologique du risque en pollution atmosphérique (1)

John A. HOSKINS (*)

RÉSUMÉ

L'opinion publique s'inquiète de plus en plus au sujet de l'environnement mais beaucoup de ces craintes proviennent de l'ignorance et de journalistes mal informés. Il est à regretter que la responsabilité en incombe plus aux experts qu'aux journalistes. Le problème se pose lors de l'extrapolation des effets observés d'une exposition à haute dose à une toxine, aux effets prévus d'une exposition à faible dose. Cette extrapolation est toujours nécessaire pour ceux qui tentent d'estimer le risque d'exposition à des toxines à des doses couramment observées dans l'environnement. L'évaluation du risque en pollution de l'environnement commence souvent par une étude toxicologique d'une exposition à haute dose, généralement d'origine professionnelle ; elle est scientifique, a de fortes chances d'être correcte et même remarquable. Il est regrettable que, dans beaucoup de cas, l'étude finisse par produire un chiffre estimé qui ne peut être ni correctement justifié ni scientifiquement validé. Malheureusement, les dernières étapes du processus d'évaluation font rarement l'objet d'un examen critique et indépendant. Comme c'est la dernière ligne qui est publiée par les média, l'opinion publique exprime une inquiétude non fondée qui peut conduire les pouvoirs publics à adopter une réglementation encore plus sévère.

A l'heure actuelle, un nombre croissant de composés qui polluent l'environnement font l'objet d'une évaluation du risque et des niveaux d'exposition acceptables ou

ABSTRACT

There is increasing public concern about the environment much of which is fuelled by uninformed journalism and ignorance. Regrettably much of the poor information comes from the professional risk assessors rather than the journalists. The problem is the extrapolation from the observed effects of high dose exposure to a toxin, to, predicted effects of exposure to a low dose. Such extrapolation is invariably necessary fro those who attempt to assess the risk of exposure to toxins at the levels generally found in the environnement. Risk assessment of environmental pollution often starts with a toxicological survey of high dose exposure, usually occupational, which will be science based, almost certainly sound and may be laudable. Regrettably in many instances the process finishes with a speculative figure which cannot be properly justified or scientifically validated. Unfortunately, the steps of the final assessment process rarely undergo independant critical examination. Since, it is the bottom line that is quoted by the media unnecessary concern is then expressed by the exposed public which can lead to ever more stringent regulations from the politicians.

At the present time more and more compounds which pollute the environment are being risk assessed and permissible or ideal levels of exposure to them set. These levels are often unjustifiably low. It is time surely to take stock and try to regain a grip on reality. Points to consider are : background levels of chemicals, death rate and

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(1) *L'article de John A. Hoskins reflète le point de vue de l'auteur et ne saurait en aucun cas engager les organisateurs des journées scientifiques ni la rédaction de la revue Pollution Atmosphérique.*

souhaitables leur sont imposés. Ces niveaux sont souvent d'une faiblesse injustifiée. Il est temps de faire l'inventaire et d'essayer de rependre contact avec la réalité. Les points à considérer sont : les taux de produits chimiques dans l'environnement général, les taux de mortalité et de morbidité de la population. Examinons-les dans l'ordre : nous vivons dans un monde chimique, nous sommes faits de corps chimiques, nous mangeons des produits chimiques. Selon les études publiées, nous respirons des produits cancérigènes, nous en produisons dans notre corps, nous en excrétons, nous en mangeons. L'évaluation des risques de l'environnement prévoit la mortalité attendue résultant de l'exposition à certains niveaux de polluants. Quand on étudie l'ensemble des polluants, on ne trouve pas assez de morts pour rendre compte de leurs effets estimés. Troisièmement, la maladie : il est difficile de la mettre en relation avec la pollution dans une population qui est en meilleure santé, en meilleure forme et d'une plus grande longévité que la génération précédente. Rien de tout cela ne signifie que la pollution est une bonne chose ou qu'elle est sans importance. Tout au contraire, elle demeure le fléau qu'elle a toujours été, en particulier dans la vie urbaine. Le message est qu'il vaut mieux ne pas faire d'estimations qui ne peuvent pas être justifiées. Elles effrayent les gens, elles peuvent causer des dommages économiques et lorsqu'on les considère dans leur ensemble leur absurdité se révèle et peut déconsidérer la science. Enfin, considérant le train où vont les choses, si les niveaux d'exposition sont fixés à des taux excessivement bas, comment sera-t-il possible de les revoir à la hausse ? Quelle commission de sages osera, à la lumière de nouvelles preuves, affirmer qu'un composé est moins dangereux que ne l'avait décidé la commission précédente ?

ill-health in the community. Take these in order. We live in a chemical world, wae are made of chemicals, we eat chemicals. According to the literature we breathe carcinogens, we produce carcinogens in our bodies, we excrete carcinogens and we eat carcinogens. Environmental risk assessment suggests the expected death rate for exposure to certain levels of pollutants. When all the pollutants are considered together there are not enough dead bodies to account for all their assessed effects. Thirdly, ill-health : difficult to relate this to pollution in a population which is healthier, fitter and longer-lived than the generation before. None of this is to say that pollution is a good thing or that it is unimportant. Quite the opposite, it is still the scourge, particularly of urban living, that it has always been. The message is rather to not make assessments that cannot be justified. They frighten people, they can be economically damaging and when taken together their absurdity is revealed which can bring real science into disrepute. Lastly, looking at the way the world works, if exposure levels are set at unrealistically low levels what is the chance of them ever being adjusted upwards? What committee of wise men will dare to say, even in the light of new evidence, that a compound is less of a danger than the previous committee decided it was?

Introduction

A foundation stone of toxicology is the often quoted, often plagiarised, statement by Paracelcus that says in essence everything is a poison depending on the dose. Unfortunately, that very important part of the statement, the dose, is often forgotten. We will happily eat a meal containing several grams of sodium chloride aware that this may be some 1% of the lethal dose but a trace of, say, a pesticide, in food causes alarm. This trace may be less than a billionth (10^{-9}) of the dose which could have any effect, a fraction so small that it is beyond the ken of the general public, but that it is there at all is enough. This attitude spills over into the general perception of many chemicals that add to air pollution. Just as weeds in a garden are really plants in the wrong place so pollutants are chemicals in the wrong place. However, public concern about the environment, often fuelled by uninformed journalism and ignorance, damns the very word « chemical » as if it were the devil returned. Air pollution is by definition unpleasant and may be dangerous. There are occasions when the air is so polluted, or when the concentration of a single pollutant is high enough to cause death. High levels of particulate matter in cities are, at the present time, believed to cause death based upon epidemiological studies while the best example of a single chemical causing death is undoubtedly carbon monoxide. Because air pollution can have such dramatic effects we have now reached a situation that when any chemicals are identified in the air, regardless of concentration, there is alarm. Regrettably, the situation is not defused by the professional risk assessors who adopt a stance which first, laudably, says that pollution, usually urban pollution, must not get any worse, and then defines the *status quo* as an upper limit that should be improved upon.

Toxicology at low doses

There is a major problem in trying to predict the effect of air pollution, or to make a risk assessment, and that is the extrapolation from the observed effects of high dose exposure to a toxin to any effects of exposure to a low dose. Extrapolation is invariably necessary for those who attempt to assess the risk of exposure to toxins at the levels generally found in the environment. Additionally, there is the piece of wisdom which, although scientifically indefensible, is adhered to on the grounds of prudence : that there is no safe limit for a genotoxic carcinogen. It is worth exploring both of these tools of the risk assessors art. Consider, for

example, the non-genotoxic carcinogen asbestos. This material is ubiquitous in the environment and occurs throughout the developed world at a level in the air of about 0.0001 to 0.001 fibres/ml. That is, we inhale about one fibre with every breath. A judge displaying his ignorance of toxicology once stated that : one fibre can kill. It is most improbable that this is so : there is no scientific evidence to support such a statement. Applying his logic to simpler chemical species and using a « linear » model, even one which is strictly only linear for low doses, would imply, *reductio ad absurdum,* that one molecule can kill.

Studies of asbestos toxicity in which animals are made to breathe an aerosol of the most toxic asbestos species, crocidolite, have shown that high levels are necessary to induce cancer in the animals. Clearly there is an apparent no effect level corresponding to many billions of fibres respired throughout a lifetime exposure. Ambient levels of crocidolite are below 0.0001 fibres/ml at which level we cannot detect an increase in the tumour mesothelioma used as a marker for asbestos exposure. Other airborne particulates which are not proven carcinogens can, in high concentrations, produce other pathologies. In the case of mineral dusts these are fibrosis and associated degenerative conditions of the lung. There is no evidence, epidemiological or from animal experiments, that exposure to very low levels of mineral dust of fibres produceds any disease at all. This is not surprising since the evolution of species on this planet as air-breathers had to cope with the fact that air contains dust and the clearance systems of the lung have developed to be efficient at removing it.

Like asbestos the majority of chemicals are not genotoxic, nor do they give rise to genotoxic chemicals on metabolism. Tumours arising from non-genotoxic materials tend to result following high doses which produce cell death and subsequent cell replacement. Such tumours may include the so called « overload » tumours [Hext, 1994]. Non-genotoxic chemicals are unlikely to be present as air pollutants in such quantities that they could produce tumours though exceptions would be exposure to the very high levels that have sometimes been found occupationally.

The second point, that there is no safe limit for genotoxic carcinogens, is difficult to demonstrate or refute by epidemiology since there is no positive effect of exposure to low levels which stands out from the background and a negative effect is not proof. It is a matter of fact that, in the UK, the areas of highest radon concentration are also the areas of lowest lung cancer. This is essentially a negative finding and so does not counter the argument. A recent study of human mortality data derived from victims who survived radiation exposure shows that in every case life expectancy is higher and cancer mortality is lower for exposed populations than for control and general populations [Kondo, 1993]. Similar experiments can be carried out *in vivo* with other carcinogens to obtain the same result [Abelson, 1994 ; Monro, 1994]. It is difficult to think of a plausible biological reason for the « no safe limit » while a reasonable explanation, the induction of repair enzymes, can be given for the alternative view. There are now so many examples in the literature that refute the dogma that the only excuse that can be given for continuing with it is prudence.

Toxicology of environmental pollutants

Not all air pollutants of concern are carcinogens and health problems arising from air pollution probably only result from exposure to a few chemical species. Acute poisoning from a number of gases or volatile toxins can cause death, but most of these could only be experienced in an occupational setting. The majority of chemicals in the air, away from the industrial setting, probably have little effect on health at all. The biggest domestic killer is carbon monoxide. This is a gas to which every city dweller is chronically exposed but which at low level appears to have no health sequelae. High levels can occur in the home through incomplete combustion of fuel and in the UK there are about 35 deaths per annum from this gas. An equally serious consequence of exposure to pollution is cancer. However, few air pollutants are carcinogens but heavy exposure on only one occasion to one of these chemicals, which would presumably be occupational exposure, could result in cancer decades later. Exposure to the low levels of, say, benzene or 1,3-butadiene found in cities are, in the UK, below levels, at which it believed they have any effect. In the case of 1,3-butadiene three orders of magnitude below. However, the chemical and epidemiological evidence of health effects is only a starting point for the risk assessment process.

It has been accepted for a long time that the periodic air pollution known as smog can pose a serious threat to health and legislation has been put in place to control it. To quote examples not too historically distant, the major cities of Scotland : Edinburgh and Glasgow, had clean air acts in place [Smoke Nuisance, 1857, 1865] nearly a hundred and fifty years ago a hundred years before the English Act [Clean Air Act, 1956] which, incidentally, repealed the earlier Acts. In 1930 when the Meuse valley in Belgium was blanketed by smog following four days of stable weather conditions 60 people were said to have died as a result. The dead were generally elderly with existing cardiorespiratory conditions and subsequent investigation blamed sulphur dioxide and related compounds for their death [Townsend, 1952]. Thousands of acute deaths were caused by the infamous « pea-soupers », as the smogs of London were known, which the legislation of the Clean Air Act successfully

stopped [Ministry of Health, 1954 ; Spedding, 1974].

Today, with a reduced use of high sulphur coal, such « oxidised » smogs are hopefully things of the past, at least in most countries of the developed world. The major outdoor problem we face now is « reduced » smogs from photochemical oxidation of, largely, vehicle emissions. Air pollution whether from smog or airborne particulates is still a killer even if the victims are those with existing cardiovascular disease [Kinny & Özkaynak, 1991 ; Dockery et al., 1993]. The association between these pollution episodes and the toxic consequences of them resulted from epidemiological studies. There is particular interest at the present time in particle pollution and arcane symbolism such as PM_{10} is now seen in newspaper headlines : at the end of 1990, environment ministers of the EC set a limit of for diesel engines of 140 mg/m^3 of exhaust emission to come into force in mid-1992. Germany, with extensive experience of diesel design, wanted a lower limit of 80 mg/m^3 and wanted to bring in tax incentives to back up this lower level. This is misuse of assessed limits to gain financial advantage.

Risk assessment of environmental carcinogens

What about airborne pollutants whose reputation rests on their genotoxicity in animal studies or the effects of high-dose occupational exposure ? Risk assessment of such pollutants at levels found in the environment starts with a toxicological survey of high dose exposure which will be science based. Consider the process for the two compounds of current concern, benzene and 1,3-butadiene, mentioned above. In the UK there is an expert panel on air quality standards (EPAQS) which makes risk assessments on chemicals which may contribute to air pollution. Consider first benzene : acute exposure to levels over 1000 ppm can be fatal and there is little doubt but that it is a human leukemogen [Krstic, 1994]. It has been shown to be carcinogenic in rats and mice given high doses (> 100 ppm) but uncertainty surrounds its low-dose toxicity in these species (ca. 10 ppm) [Cronkite et al., 1989]. It has been concluded that the risk of leukaemia in exposed workers is not detectable when average exposures over a working lifetime are around 500 ppb [EPAQS : Benzene, 1994]. This is a conservative estimate and relies in part on averaging industrial exposures over a working lifetime. This idea, that low exposure to a genotoxic carcinogen over a long period of time is more important than peak exposure appears in other UK government publications [AIR QUALITY, 1995]. Not surprisingly there is no scientific justification for this statement and probably there never can be. The same method is employed in the study of 1,3-butadiene for which it is concluded that no increased risk of lymphomas and leukaemias would be detectable by any practicable means in cohorts of workers exposed to 1000 ppb over a working lifetime [EPAQS : 1,3-Butadiene, 1994]. The above levels are for those occupationally exposed. To translate them into figures applicable to the whole population who are environmentally exposed they are reduced to a tenth of their value since working life is approximately a tenth of chronological life. The next step is the application of a safety factor on the grounds that there may be individuals who are particularly sensitive to the compound or who may be exposed to other carcinogenic compounds with which there could be additive effects of synergy. This factor is often taken to be 10 unless the result produced is patently absurd in which case some other factor, say 2.5, might be preferred. This latter factor is often expressed as 10^4 to give it greater weight. For benzene and 1,3-butadiene the safety factor was chosen to be 10. Also, for both these compounds the epidemiological data was considered adequate (but see below). If this had not been the case, as with many other compounds, and the only good data had come from animal experimentation, then a further factor to allow for the difference in sensitivity between species would have been applied. This factor is usually 10 often regardless of any data which could suggest that rodents might be the more sensitive species.

The above assessment for benzene gives an air quality standard of 5 ppb. Rural levels have been shown to vary in a periodic fashion between 0.5 and 2.0 ppb with the greater concentrations in the winter Levels in Greater London are higher and a winter peak up to 13 ppb was measured in the winter 1991/2. Thus, the level set is comfortably above the present rural levels, but uncomfortably close to average present urban levels. There is a consensus that urban air is of poor quality and therefore a further recommendation that the level be reduced in time to 1 ppb was also proposed. Science has been deserted long ago and this is obviously a political stick with which to beat the government to try and make it legislate to improve the quality of urban air through the control of motor vehicles. The reasons behind setting the standard for benzene look even shakier when applied to 1,3-butadiene. First divide by 10, then divide by 10 again to obtain a value of 10 ppb. But, ambient levels are rarely higher than 1 ppb except at the urban kerbside. This should have been a matter for rejoicing but it was not. A level so much greater than ambient could not be acceptable and so it had to be divided by 10, yet again, to give the current standard of 1 ppb. The « Alice in Wonderland » reasoning for this was that it was felt that the epidemiological data was weak. Put another way, little effect of high industrial exposure has been found. Since many workers have been exposed this might suggest to some that the compound was of low carcinogenicity : apparently this is not so.

Conclusions

It is important to realise that the risk implied in the setting of the standards should not be interpreted as real since the scientific evidence does not support this conclusion. Rather it is a political, or possibly even an ethical, consideration which carries through the *ad hoc* process. Surely, risk should be the likelihood, or probability, that the toxic properties of a chemical will be manifest in populations of individuals under their actual conditions of exposure ? This is not the same as the risk assessment in which the end result has to be close to the *status quo* by prescription so that the best that can be said at the end is : adequate but could do better.

It is regrettable that in many instances the process of risk assessment for environmental pollutants starts with good toxicology but finishes with a figure which cannot be properly justified or scientifically validated. It is equally unfortunate that the steps of the final assessment process do not undergo the same critical examination as the factual evidence. Since, it is only the bottom line that is quoted by the media the result can be unnecessary concern for the exposed public and this can lead to voter-wary politicians supporting ever more stringent regulations.

Desirable levels or air quality standards can be set unjustifiably low. It is time to take stock and try to regain a grip on reality. We must not get into the situation in which every thing is either risky, carcinogenic or simply proscribed. If we do then the rules, regulations and warnings will be regarded in the same way that the wording : « known to the State of California » is today. The background levels of chemicals are generally low, the death-rate does not exceed the birth-rate and in the developed countries ill-health in the community continues to decrease. We live in a chemical world, we are made of chemicals, we eat chemicals. According to the literature, we produce carcinogens in our bodies, we eat carcinogens and we excrete carcinogens from probably every orifice. Environmental risk assessment proposes a number of deaths following exposure to pollutants. However, when all the pollutants are considered together there are not enough dead bodies to account for all their assessed effects. None of this is to say that pollution is a good thing or that it is unimportant. Quite the opposite, it is still the courge, particularly of urban living, that it has always been. The message is rather to not make assessments that cannot be justified. They frighten people, they can be economically damaging and when taken together their absurdity is revealed which can bring real science into disrepute. Lastly, looking at the way the world works, if exposure levels are set at unrealistically low levels what is the chance of them ever being adjusted upwards ? What committee of wise men will dare to say, even in the light of new evidence, that a compound is less of a danger than the previous committee decided it was ?

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