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November 16th 2006

The Honorable Stephen L. Johnson
Administrator
US Environmental Protection Agency
1200 Pennsylvania Avenue
Washington DC 20460

Re Draft Advisory Report of US Science Advisory Board on Carcinogenic Effects of Arsenic

Dear Mr Johnson

I apologize for some haste in presenting this "comment". I have had medical and other disasters that have prevented me from spending much time before your deadline.

This report needs fundamental work before it should be presented to the public as an EPA document. This report, if accepted, will become a part of EPA policy and since most regulators and the public have a short term memory of 3 years or less, earlier reports will be ignored unless specifically referred to. I suggest that be done. A part of the problem is responding to a set of questions in the charge that imply matters not addressed. These questions are also badly worded making the work of SAB very difficult and all the more important

In my view the crucial question is: "what should be used as the dose response relation at the low doses to which the US public are exposed?" IT SHOULD BE ASKED AND ANSWERED DIRECTLY

Nowhere do I find the statement of EPA policy in this regard dating back (at least) to 1975. Arsenic is clearly carcinogenic to humans. It produces a number of cancers that also occur naturally. No pathologist has yet been able to distinguish between a naturally occurring cancer and (from evidence of dose obtained by someone else) a cancer believed to have been caused by arsenic. It seems likely that they are fundamentally indistinguishable. Then the default of 1975 should apply. A dose response that is linear through zero (proportional) should be the default. This statement is independent of the series of stages through which the cancer formation may progress. I note also that this view is implicit in the formulation of the multistage theory of cancer as formulated by the late Sir Richard Doll and Armitage 52 years ago and repeated by Sir Richard Peto many times since 1970. The issue might be below what level should that linearity be assumed? I use as a rule of thumb that it should be below any cancer rate where half is due to natural causes. Others might disagree but it seems incumbent to explain what is wrong with the Richards' arguments. The default might until arguments and data come up. But none have come up in the last few years. This should have been carefully discussed in the formulation of questions D 1- D5 and in the Panel Answers. It might be different for bladder cancers, where the naturally occurring cancers exceed the (calculated) arsenic cancers at fairly low level - at about 100 ppb in USA - and for lung cancers where, in USA, the natural level is dominant. If low dose linearity exists even for one cancer, the risk of that cancer will dominate at low

enough doses. So any answer to any questions must either subsume Feynman's "paradox", or explain why not. I find neither in the draft. It should be added. IT WA NOT. UNLESS THIS PART IS FUNDAMENTALLY MODIFIED THE WHOLE REPORT WILL BE AND SHOULD BE DISCREDITED.

I attach my comment to the EPA on an earlier request for comment.

I have not examined carefully the data in the answers to questions A1, A2 and B1. But these fail to make the basic point that using the "usual" animal to man comparisons of carcinogenicity, arsenic has always been an exception. Animals do not get cancer as much as the human data suggest. Unless this is clearly expressed, we have no basis for using animal data. I am glad that the SAB do not come out with a suggestion that we do. I hope that it will change, but we are far from being there yet. I had hoped that this would come out more clearly.

Charges B2 and B3 seem sensible.

Charge C1(i) and C1(ii) as noted above there are no existing fundamental animal to man comparisons that seem to work for arsenic in the environment. There exist no data for DMA alone on humans and it may be that the risk is small enough that the "usual" animal man comparison would work. But this is not addressed by either the EPA questioner or SAB and the fundamental problem is thereby ignored

Question C2 is reasonable. But again the questioner and the SAB ignore two fundamental points. Firstly it is not sensible scientifically and probably not valid in law to depend upon a single data set unless it is outstandingly good. The Taiwan data set is not. In 1986 when the Taiwan data came out it was widely disbelieved. Indeed if there were no other data it is probable that it would still be disbelieved. The panel only partially addressed this in (ii) of their answer. But they did NOT state the fundamental point that at low doses, where the risk is 1% or less (compared with the 10^{-6} that the EPA like to use) it is impossible to derive a dose response. ALL THAT CAN BE DONE IS ASK WHETHER A SPECIFIC DOSE-RESPONSE MODEL IS WRONG OR NOT.

SAB request, in Charge D2, specific epidemiological studies at low doses. In the document (page 49) they incorrectly discuss one such study - Lamm et al. 2004. Worse still, it appears that they behaved unscientifically in criticizing this study which has been in the refereed literature for 2 years. It is well known that editors usually demand a size reduction so that much useful information is not incorporated. But a simple enquiry from the authors can elucidate the matters at issue. I have checked with the other authors and it seems that NO SUCH ENQUIRY WAS EVER MADE. This must be corrected in the final. Also, since the SAB (somewhat dubiously as noted above) insist that the Taiwan data should be used to derive the dose response such criticism should be made on that data set too. Specifically:

1. It is important to clearly state any assumptions in the statistical analysis
2. Both are ecological studies and it is well known (ALTHOUGH IT SHOULD BE RESTATED) that it is mathematically IMPOSSIBLE to derive a dose response relation from data connecting average cancer rate with average dose.
3. If the aim is to decide whether the data SUGGEST a low dose linearity or a threshold the data should be analyzed using parameters that address this point. Mathematically it can be shown that if low dose linearity is correct the slope is given correctly if average cancer levels are plotted against average concentrations in each bi. For that reason Lamm et al published a data using average concentrations (not median concentrations as SAB incorrectly state) although similar conclusions can be, and were drawn from the unpublished analysis using median concentrations. In the paper on the Taiwan study which was, I

understand, the EPA relied on (although the EPA record is unclear on this), Morales et al. used MEDIAN exposure levels which is clearly inappropriate for discussing an assumed linear dose-response

4. A straight line plot through the origin using ONLY the uncertainty of statistical sampling of the data is NOT a good fit for either the Taiwan data or the Lamm et al study. Lamm et al commented on this; the analyses of the Taiwan data (except one not referenced by the EPA and presumably not noticed) did not. Lamm et al noted that to get a good fit one would have to assume a variability (for unknown reasons) between counties, equal to that of the statistical sampling uncertainty of about 15 cases. For this reason they presented an analysis leaving out the counties with the smallest number of cases, leaving the weight only on a county basis. It would be possible, to redo the whole analysis by assigning each county weighted by adding in quadrature the sampling uncertainty and a variability from unknown causes that is county independent. They also commented that any improvement on such analyses must include a reason for the variation between counties that would enable the statistical power to be utilized.

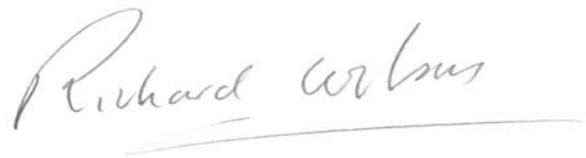
SAB SHOULD NOTE THIS TOO. ALSO AT A MINIMUM EPA SHOULD

COMMENT UPON THE THREE PAPERS IN THIS REANALYSIS OF THE TAIWAN DATA SET by Lamm and others.

5. Neither the Lamm et al 2004 study nor the Taiwan study have a good idea of the migration and out migration. This could be a systematic error lessening the slope of the calculated dose response relation. Since there appears to be a large variation between townships in the Taiwan data the migration need not be very far for this to be important. However this point is not clear in the SAB criticism of the Lamm et al 2004 study AND MUST BE DROPPED OR STATED MORE CLEARLY. As stated in the paper, counties were chosen where 90% of the residents got water from ground water. The average level (NOT THE MEDIAN) was correctly stated.

6. Both the Lamm et al. 2004 studies and the unmentioned reanalysis of the Taiwan data clearly show that there are uncertainties in the values at each exposure grouping that exceed the statistical uncertainty of the number of cases. But I state here my comment on all reanalyses. There is a fundamental problem, rarely addressed in reviews like this, that any attempt to discuss a question, not clearly posed in advance, has statistical problems that may even completely invalidate the conclusion. The Nobel Laureate Richard Feynman clearly addressed this in his elementary physics lectures when he discussed the probability of seeing a specific car in the parking lot. I have written about this as applied to epidemiological studies, and scientists often call the problem "data dredging". Unless there is a clear discussion of this (which I have not seen and do not believe exists) I would stick with the claim that the problem of the EPA analysis of the Taiwan data exceed that on the Lamm et al 2004 analysis of the county data.

5. Lamm et al. 2004 did not claim to demonstrate any particular dose response relation. They made one important claim. That the slope of a straight line for bladder cancer from high dose data through the origin was statistically excluded. BUT they could not exclude the straight line, calculated by EPA. That claim should be directly addressed.

A handwritten signature in cursive script that reads "Richard Wilson". The signature is written in dark ink and is positioned to the right of the main text block.

Yours sincerely,

Richard Wilson
Mallinckrodt Research Professor of Physics

Default Dose Response Relationships for Lesions caused by Chronic Arsenic Poisoning
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Presented to the US EPA as a public comment upon the arsenic regulations proposed on Thursday June 22nd. Modified from a poster presentation at the 4th International Arsenic Conference, San Diego, June 2000 and modified from a presentation to the Science Advisory Board of EPA on June 9th 2000.

Introduction

In considering a possible dose-response relationship it is important to distinguish two possible cases. Firstly a situation where the lesion has a unique cause, and second where the lesion is indistinguishable from a lesion that occurs naturally. Arsenic caused lesions are of both types. The skin lesions, dyspigmentation, keratoses and perhaps skin cancers all seem to be unique, whereas the internal cancers, lung, bladder, kidney and liver are indistinguishable from other cancers.

Historical

That chronic arsenic poisoning causes skin lesions was reported by Hutchinson (1887,1888) but was widely ignored until Tseng et al. (1965) found skin lesions, "blackfoot disease" and skin cancers, in Taiwan which he attributed to arsenic exposure. Tseng's work has been analyzed and reanalyzed many times. The result of one such reanalysis (Byrd et al. 1996) is shown in figure 1. The skin cancer rate is plotted against the average concentration in the water. It clearly shows a either a non-linearity or a threshold (hockey-stick) behavior with a threshold at about 130 ppb in the water.

Tseng's data are merely an "ecological" study, because only average rates are plotted against average concentrations. It has been criticized both on this ground and because the attribution to arsenic may not be correct. However skin lesions (other than blackfoot disease) have been seen among arsenic exposed people elsewhere - Inner Mongolia for example. Recently the individual outcomes and concentrations for 3000 villagers were followed (report of IMCAP to ATSDR 2000). These, plotted in figure 2 show a threshold when the probability of a lesion is plotted against concentration, at 50 ppb for dyspigmentation or keratoses and 300 ppb for skin cancer. Taken together we suggest that these data suggest an appropriate dose response relationship for skin lesions is a hockey stick function with a threshold above 50 ppb.

Although it is desirable to check this conclusion in other cohorts, especially since skin lesions might behave somewhat differently among different races, there seems little reason to doubt that there is a threshold, or at least a gross non-linearity, for the production of skin lesions.

But the situation for the internal cancers is very different. In a couple of papers which surprised most scientists, Chen and collaborators (1985,1986) showed that there is a considerable increase in mortality from internal cancers among those who drank water from the arsenic laden wells in Taiwan. Again these data have been analyzed and reanalyzed. Byrd et al show plots of rates of various internal cancers plotted against average concentrations. The plot for bladder cancer in men is shown in figure 3 and for total cancer

mortality in figure 4. Again conclusions from these data must be tentative because it was an "ecological" study. But the cancer rate when plotted against concentration shows an excellent fit to a straight line with no threshold - in contrast to the situation with skin lesions. This suggests (but does not prove) that internal cancers behave very differently, and may have a different mechanism, from skin cancers.

More recently, case control studies have been performed in Chile (Ferreccio et al. 1998) and Argentine (Hopenhavyn-Rich et al., 1996,1998) which show unequivocally a large increase in bladder, kidney and lung tumors with arsenic concentrations in water of 500 ppb. Figures 5 and 6 (taken from Professor Allan Smith's report to WHO) shows the data for bladder cancer and lung cancer each with a straight line from the Taiwan data superposed. Although the line fits the data adequately, inadequate statistical accuracy in distinguishing an effect from a background prevents finding effects at much lower levels so that the dose-response has to be judged from indirect data or general principles.

Relating cases to natural background

Crowther (1924) suggested a simple single stage model for radiation induced carcinogenesis whereby radiation ionizes a cell that replicates and leads to a cancer. In its simplest form the theory leads to a linear dose response relationship. But his theory was obviously incomplete early on. Cosmic rays ionize thousands of atoms in the body each second. There must exist some mechanism, repair or excretion, that prevents all but one in a billion ionized atoms from proceeding to form a tumor. Nonetheless it is widely, but erroneously, believed that only mutagenic compounds can lead to a linear dose relationship. The initial step of modifying a cell to start a tumor is probably only one step in cancer formation and any step can be modified. Indeed the idea of the 1970s that genotoxic materials are especially carcinogenic and only genotoxic materials can give a low dose linearity runs into many troubles and cannot be sustained as a general principle. It is likely that the major action of even genotoxins in the environment is to promote a cancer already initiated by natural processes.

The multistage models, although originating in the 1930s were developed by Doll and Armitage (1954, 1957) to describe the distribution of cancer as a function of age. To do this they found that it was necessary to consider that cancers develop in 4 or 5 stages and that each stage may be influenced by a different biological mechanism. In applying the model to cancers caused by anthropogenic activity they suggested that one (or at most two) stages be influenced by pollutants. Inherent in this description was the assumption that this influence would act in the same way as whatever in the background influenced this stage.

It was evident in 1954 that, given this assumption, at low doses of pollutants that the effect would be linear with dose and effects of different pollutants would add. But at high doses, a multiplicative synergism between two pollutants would naturally occur as the probability of a stage exceeds the background probability in two separate stages. According to these ideas, therefore, non genotoxic substances are as likely to lead to a linear dose response as genotoxic substances.

Crump et al. (1976) and Guess et al. (1977) pointed out that the argument for low dose linearity is far more general than the Doll Armitage theory and depends solely on the fact that cancers caused by the pollutant and natural (background) processes are indistinguishable and therefore it is likely that the pollutant and the background act in a similar way at some stage in the cancer induction process. Crawford and Wilson (1996) showed that the argument is even more general and applies to a wide variety of non-cancer outcomes.

These analyses were used by US EPA 25 years ago as a justification for assuming low dose linearity as a general default. But the issue arises how to derive the low dose slope from high dose data. Unfortunately EPA's attempts confused the issue. Their use of the words "Linearized MultiStage (LMS) model" implied more biological and mathematical justification than existed. Zeise et al (1987) objected in vain and proposed that they more honestly say "truncated polynomial model". More recently Cox (1997) and Chiu et al. (1999) have produced a most welcome precise mathematical formulation.

These general ideas should therefore be used to suggest a dose-response relationship for the internal cancers produced by arsenic. The default will then be linear at low doses. When combined with a desire of the US EPA to regulate any (lifetime) risk larger than one in a million there are difficulties. The dose for a one in a million risk is between 1 and 5 parts per trillion when lung, kidney and bladder cancers are all included. Background levels exceed this by a factor of 1000! This then is the core of the problem regulators have faced for the last 14 years in considering the standard for arsenic in drinking water.

There is general agreement that one should use "scientifically motivated risk assessment" whenever possible, although there is far less agreement about what that means. I contend that the general (default) arguments above are very scientific. What data, direct or indirect, might be obtained to move away from the default? In this problem I find that most of the discussions of toxicologists are not helpful since they fail to discuss the natural processes at the same time as they discuss their ideas about arsenic related processes. Indeed the whole world was misled by a misunderstanding of animal toxicology. Rats and mice cannot (easily) be persuaded to get cancer from arsenic. Ergo, men cannot get cancer either and for a century (1888 to 1986) data that suggested otherwise (albeit with small statistical samples) were discounted and thought to be in error. The task for a toxicologist who wishes to depart from the linear default is a daunting one. It is insufficient for him/her to have a theory that describes how arsenic produces a cancer, unless that theory also describes how the natural cancers occur and whether there is a difference. I am unaware of any such complete description.

But an important purpose of the mathematical models must be to point out where scientific (usually biological) data will be most useful in elucidating the low dose behavior. Statistical sampling errors would prevent any direct demonstration of a threshold in internal cancers if such a threshold were at 50 ppb or below. But we can ask an indirect (but leading) question. Are internal cancers always preceded by, or accompanied by, a skin lesion? As stated the answer must be no. For with no arsenic exposure at all (natural background) there exist internal cancers. But I note that at arsenic levels of 500 ppb the rate of skin lesions is only about 20%. Then we can modify the question: "at 500 ppb is the increase in internal cancers solely among those with skin tumors, or is it also among the larger group of persons without skin tumors?" If the former, then I would argue that the dose response for the internal cancers might well follow that for the skin lesions and show a threshold. For example, if the ideas of Dr Menzel presented at the 4th International arsenic conference at San Diego are correct I would expect just such a difference in the epidemiological studies. It is of course important to select in a blind fashion, persons with the 500 ppb exposure BEFORE asking whether or not they have skin lesions or internal lesions.

This question is very similar to that asked by Dr Mereweather, Chief Inspector of Factories in UK in 1938. "Is it asbestos, or the asbestosis caused by asbestos, which is the cause of the lung cancers? For if the former, a linear dose response relationship is likely from the Crump et al. arguments, if the latter then a threshold is probable. It is also similar to the question asked about benzene: "are the leukemias caused by benzene always preceded by pancytopenia or not?" For if the former, a threshold is probable. I note that neither in the asbestos case nor in the benzene case has a definitive answer yet been forthcoming, and EPA assume the linear default.

How should society cope with default linearity?

The above merely notes what a default risk assessment might be. It should not by itself be used to argue for any particular level for an arsenic standard. I note that if the default linear dose response applies to radiation induced cancers also, as is often believed, in spite of Dr Cohen's studies that show unequivocally that lung cancer rates are LOWER in counties with high radon levels than in counties with low radon levels, then the lifetime risk at the level of the natural background radiation is about 0.2%. This is about the risk of arsenic at a 5 ppb concentration of arsenic in the drinking water - including a water equivalent of arsenic in the foodstuffs. Neither radiation nor arsenic can be regulated at a one in a million level. As I have stated publicly many times in the last 21 years EPA cannot do so consistently. Their attempts to do so are arbitrary, capricious and possibly illegal. Society, Congress representing the society, and EPA executing the will of Congress, must come to grips with this issue.

Since society has coped moderately well with radiation, I suggest that regulation of arsenic should follow similar rules. Many years ago the International Commission on Radiation Protection (ICRP) proposed that average anthropogenic radiation doses to the public be kept below 170 mrem/year, although individuals might reach 500 mrem/yr. 500 mrem/yr adds a risk, assuming a linear no threshold theory with the usual slope of nearly 1%. In order to achieve this society has set a few rules, such as the NRC rule that radiation levels at the site boundary of a nuclear power plant should be kept less than 10 mrem/yr. But the main rule is As Low As Reasonably Achievable (ALARA) which could apply to arsenic (and many other pollutants) also. This was interpreted (although not yet applied very often) by NRC (1976) as meaning that society should spend \$1000 per Man Rem on reducing exposure, (updated in 1992 to account for inflation and political correctness) to \$200,000 per person Sievert and the implication (not always followed) is that ONE SHOULD NOT SPEND MORE. Using a slope of an assumed linear dose response of one fatal cancer per 30 Sv a linear dose response and the usual slope, this corresponds to about \$6,000,000 per calculated cancer averted. I note that this is about the same as the \$4,000,000 per statistical life that EPA proposed in summer 1998 for cost benefit calculations but a little less than EPA proposed in discussion of the proposed arsenic standard.

Although it has been said that consistency is a refuge of small minds, it is worth enquiring what consistency between regulation of radiation exposure and of arsenic exposure would entail. For arsenic, a literal following of ICRP would lead to an acceptance of 50 ppb as a principle, with rules to keep individual exposure from single large facilities below 1 ppb. An ALARA principle could be that one should spend a sum of \$1,000,000 per person-ppb to reduce arsenic exposure. (At a concentration of 1 ppb the risk is about 25% and 25% of \$4,000,000 is \$1,000,000). The 1996 Amendments to the Safe Drinking Water Act (SDWA) for the first time explicitly granted EPA discretionary authority, if it determines that the technically feasible level does not justify the costs, to adjust the standard to a level that maximizes health risk reduction benefits at a cost that is justified by the benefits. Now that this discretionary authority exists, there seems to me no good reason why the EPA should not use cost explicitly in the discussion of alternatives and come into line with the thinking of risk analysts world-wide and recent thinking of other regulatory bodies.

Voluntary compliance

It is clear that the main cost burden of nation-wide compliance with a reduced arsenic standard will fall upon some small towns in the western states. At the 4th International arsenic conference a representative from a small California town complained about this. But if he fails to meet the new standard, those affected are only his voters and not any do-gooders on the eastern seaboard. Following this line of reasoning I suggest an alternative to the compulsion that the EPA proposed on May 24th. There should be

an absolute limit of 50 ppb as now, compulsory for all. Above this level health effects have been definitively observed and below it they have not. Each water district would be at liberty to vote on whether to adopt a lower standard of 3, 5, 10 or 20 ppb and could do so if they could justify to EPA that this meets the ALARA principle. This justification would be based on the exposure averaged over time and averaged over people to arsenic laden water not the peak exposure. A standard of 50 ppb probably leads to average exposures in a community of 20 ppb. Then this economic rule suggests that a community of 1000 people should be willing to spend \$20 million to reduce their exposure below the 450 ppb standard, but not more. Since most of the water supplied to a household is used for functions such as flushing a toilet, or bathing, and since dermal absorption and evaporation of arsenic is small, a community should be permitted the option of switching to bottled water for drinking and leaving the standard alone.

Long-term disposal of arsenic

More important, however, are the long term implications of bringing arsenic from secure storage below the ground to the environment above the ground. Of course we have been doing that in mining activities for 3000 years. In Bangladesh, for example, much irrigation is by water from arsenic-laden tube wells. The arsenic can build up and cause the arsenic level in foodstuffs to steadily increase. In considering this EPA should be guided by a similar concern that has been expressed for high level nuclear waste. Here there is considerable concern that the waste is long lived, and cannot be broken down as one hopes that organic chemicals are broken down with time. Half lives of thousands of years cause concern. But I note that the half life of arsenic is infinite. Fortunately we no longer spray 40,000 tons a year (20,000 tons imported) on our crops and forget about it. But, in line with our concerns about materials which are carcinogenic solely because of their radioactivity (where we insist on accurate tracking of radioactive sources), we might insist that ANY quantity of arsenic greater than 1 gram be tracked. The arsenic, being carcinogenic for ever, should obviously be placed in a landfill at least as secure as planned (at Yucca Mountain for example) for long lived nuclear waste. In line with the EPA requirement that no one's radiation exposure be increased by more than 2 mrem per year if there is an accident at a nuclear repository, EPA should demand that no one's exposure to arsenic be increased by more than 1/4 ppb as a result of an accident at an arsenic repository. For arsenic of course this must be satisfied for ever, in contrast to the nuclear requirement of a few thousand years.

If these suggested rules for arsenic seem unreasonably stringent to you, then I suggest that you recommend to those at EPA and NRC that are considering the matter that rules for the comparable hazards of radioactive materials be modified to match whatever rules you finally adopt for arsenic.

References

- Armitage P. and Doll R., (1954) *Brit J. Cancer* 8:1-12
Armitage P. and Doll R., (1957) *Brit J. Cancer* 11:161-169
Byrd D.M. , M Luann Roegner, James C. Griffiths, Steven H. Lamm, Karen S. Grumski, Richard Wilson, Shenghan Lai, Carcinogenic risks of inorganic arsenic in perspective. *International Arch Occupational Environmental Health*, 68:484-494, 1996.
Chen, C.J., Y.C. Chuang, S.L. You, and H.Y. Lin. 1986. A Retrospective Study on Malignant Neoplasms of Bladder, Lung and Liver in Blackfoot Disease Endemic Area in Taiwan. *Br J Cancer*, 53:399-405.
Chen, C.J., Y.C. Chuang, T.M. Lin, and H.Y. Wu. 1985. Malignant Neoplasms Among Residents of a Blackfoot Disease Endemic Area in Taiwan: High Arsenic Artesian Well Water and Cancers. *Cancer Res*, 45:5895-5899.

Chiu, W.A. Hassenzuhl D.M., and Kammen, DM. (1999) Risk Analysis 19:15

Cox, L.A. (1995) Risk Analysis 15: 359

Crawford, M. and Wilson, R. (1997) "Low Dose Linearity the Rule or the Exception" Human and Ecological Risk Assessment 2:305-330

Crowther J, (1924) "Some Considerations Relative to the Action of X-rays on Tissue Cells" Proc. Roy. Soc. Lond. B Biolog Sci. 96:207-211

Crump, K.S., Hoel, D.G., Langley, C.H., and Peto, R. (1976) "Fundamental Carcinogenic Processes and their Implications for Low Dose Risk Assessment" Cancer Research 36:2973

Ferreccio C, et al Lung cancer and arsenic exposure in drinking water: a case-control study in northern Chile. Cad Saude Publica 1998;14 Suppl 3:193-8

Guess, H., Crump, K. and Peto R. (1977) "Uncertainty Estimates for Low Dose Rate Extrapolation of Animal Carcinogenicity Data" Cancer Research 37:3475-3483

Hopenhavyn-Rich C, et al Lung and kidney cancer mortality associated with arsenic in drinking water in Cordoba, Argentina. Int. J Epidemiol 1998 Aug;27(4):561-9

Hopenhayn- Rich C, Biggs ML, Smith AH, Fuchs A, Bergoglio R, Tello E, Nicolli H. Bladder cancer mortality associated with arsenic in drinking water and in Cordoba, Argentina. Epidemiology, 7:117-124, 1996.

Hutchinson, J. (1888) Diseases of the skin: On some examples of Arsenic_keratosi of the skin and of Arsenic-Cancer. Transactions of the Pathological Society of London 39:352-363, 1888.

Hutchinson, J. 1887. Arsenic cancer. Br Med J, 2:1280-1281

NRC (1975) Rule making RM-30-2

NRC (1992) Letter of Tom Kress, Chairman, ACRS, updating RM-30-2 to account for inflation and political correctness.

Zeise, L., Crouch, E.A.C. and Wilson R., (1986) "Dose response for Carcinogens: A Review" Environmental Health Perspectives 73:259

FIGURES

Alas the figures in this comment cannot be easily printed here but are available on the website:

http://Physics.harvard.edu/~wilson/publications/EPA3_2000_files/