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RISK AND DOSE: SOUND PROVABLE SCIENCE

Despite popular statements to contrary, a toxicological principle and continued scientific reality, is that the dose makes the poison. Less than a gram of purified Botulinum toxin, an amount covering the head of a pin, if evenly dispersed, would kill an auditorium full of people. Yet dermatologists and plastic surgeons worldwide inject Botulinum toxin under facial skin to ablate wrinkles. How can they do this? By diluting the agent 1 million fold.

The risk of cancer related to environmental agents is also dose-related. We know that experimental animals, such as rats or mice, will exhibit dose-related responses to carcinogens. Below certain doses, they develop no cancers. Above certain doses, cancers occur. In human beings, the best example of dose-response for cancer-causing agents is found in smokers. In smokers of 14 pack years of cigarettes, the relative risk of lung cancer (compared with non-smokers) is 4-5 fold. In smokers of 30 or more pack years, however, the relative risk is over 10 fold. (1) Thus, in the case of smoking, there is a dose relationship between the amount of cigarettes smoked and the risk of lung disease. An individual who smoked one cigarette in his life has no reported or discernable excess risk of lung cancer. Is it impossible that one cigarette in a lifetime increases lung cancer risk? No. However, all of the risk-dose relationships indicate that if one cigarette creates any risk, it would be so small as to be non-detectable in studies. Moreover, that risk is likely so low as to be *diminimis* or nearly non-existent.

The same applies to other known human carcinogens as well. In the 1970's, Askoy identified an excess risk of acute myelogenous leukemia (AML) in shoemakers in Turkey. (2) They were exposed day-in and day-out to hundreds of parts per million of benzene in the air of their small workshops. Subsequent studies have confirmed this relationship in heavily-exposed workers. No epidemiological studies, however, have shown an increased risk of AML in individuals casually-exposed to low levels of benzene. Again, if any risk exists, it is likely to be negligible.

Conceptually, and from the epidemiological standpoint, asbestos is no different. At background levels of asbestos exposure, there is no scientific evidence of, nor any scientific basis on which to assign an increased risk for mesotheliomas—one of the malignancies associated with asbestos exposure.

In a recent decision, a Pennsylvania judge addressed this issue with a thoughtful and detailed ruling. The question was: Is it enough to say any exposure to any amount of asbestos is sufficient to be a contributor to a mesothelioma? Judge Colville of Allegheny County, Pennsylvania, was not persuaded by the claimant's experts' presentation that the science permitted an affirmative answer. For the past twenty or more years, many courts have simply accepted, without careful probing, unsupported statements that any occupational exposure must be considered causal or contributory. Expressing an uncommon and refreshing understanding of the limits of scientific support for such a claim—that is, the distinction between scientific knowledge and abject speculation or personal belief---Judge Colville in the Court of Common Pleas, Allegheny County, Pennsylvania eloquently articulated the distinctions. (3)

A few of his comments, scientifically meritorious and applicable, not only to asbestos, but to benzene and any other potentially low-dose toxin exposure, are illustrative. In discussing the plaintiff's experts' opinion:

> that every exposure constitutes a proximate cause of a subsequently diagnosed asbestos-related disease—is based upon generally accepted methodologies in the relevant scientific field. In my opinion, based upon the evidence of record, it is not…. In the end, my decision ultimately rests upon whether the plaintiff's experts' opinions were based upon methodologies utilizing discrete and specific scientific principles logically applied in a manner that can be affirmatively articulated, referenced, reviewed and tested and empirically verified or whether the testimony was based upon the "best estimate," the "gut instinct," or the "educated guess" of the experts…The plaintiffs' experts' foundational opinions are based upon the latter rather than the former.

He went on:

> Specifically, I precluded Drs. Maddox and Laman from testifying that each and every fiber of asbestos is a substantial contributing factor in the development of asbestos related disease and that the specific plaintiff's disease in this case was caused by exposure to a specific defendant's friction product. I did so because I discern no generally accepted methodology within the relevant scientific field to support those opinions.

While we know that many witnesses would opine similarly, that every fiber was a probable contributor, it is clear that Judge Colville did not consider the mere frequency of opinion repetition as an acceptable methodology.

The Judge recognized another logical flaw—one in which all background exposures are discounted, but any "industrial" or "occupational" exposure is not and, importantly, how one goes about quantitating an increased risk. How much more exposure is sufficient to know that causation or contribution occurred?

> No one, including plaintiff's experts, proffers an opinion that this level of exposure creates an increased risk of the development of any asbestos-related disease. Accordingly, this background or ambient exposure is simply not sufficient to allow experts to causally attribute asbestos-related disease to it. Everyone, including plaintiff's experts, agrees that something greater is required. The argument in this Frye challenge, in part, revolves around the question of how much greater quantity of exposure is necessary to permit the causal attribution of an asbestos-related disease to a particular asbestos exposure.

He further discusses dose:

> Drs. Maddox and Laman do not rely, in any respect, upon any actual quantity or quality of exposure suffered by any specific plaintiff, but rather, conclude that if the evidence supports a single exposure, then causation can be opined and asserted. Accordingly, Drs. Maddox and Laman are required to assert than an asbestos-related disease dose response curve applies even when there is a vanishingly small exposure. I have been unable to find, and I do not believe that Drs. Maddox and Laman, or any other witness or authority offered on behalf of the plaintiffs, has offered any generally accepted methodology to support this proposition.

The discussion continues with excellent, scientifically well-reasoned arguments. (3) I invite the reader to read the entire text. While I realize that this is a lower court decision which may or may not survive an appellate review, it reflects such a clear understanding of the limits of scientifically-supportable testimony that it serves as a model for good science in the courtroom.

Judge Colville's decision can be contrasted with the prevailing *Rutherford* ruling in California which articulates jury instructions in asbestos matters (and, depending upon the outcomes of some current cases, perhaps to other toxic tort matters as well). In *Rutherford,* we have two quite contradictory statements. First, a company's asbestos is responsible, if it was "a substantial contributing factor." If this language alone were the current California law, a judge there could and should reach the same conclusions as did Judge Colville in Pennsylvania. However, "substantial contributing factor" is further defined in *Rutherford* as an exposure which "more probably than not contributed to the risk." With that qualifier, all reference to dose, to fraction of contribution, to clinical relevance is eliminated. In other words, even if it contributed 1/trillionth to the risk, it could be, and is routinely, claimed that "it more probably than not contributed" and, therefore, by the definition provided in *Rutherford*, was "a substantial contributing factor." This language makes no scientific sense whatsoever and cries out for revision.

Although Judge Colville's ruling was in an asbestos claim, its reasoning is broadly applicably to all *diminimis* exposures, for example, those seen in many of the benzene claims today. In those, it is commonly claimed that *any* exposure to even trace amounts of benzene, such as those found in any product containing a petroleum distillate, contributed to or caused a claimant's disease—usually acute myelogenous leukemia (AML). To paraphrase Judge Colville: There is no generally-accepted methodology to support this opinion.

REFERENCES

1. Godtfredsen, N.S., E. Prescott & M. Osler. (2005) "Effect of smoking reduction on lung cancer risk." *JAMA.* 294(12): 1505-1510

2. Aksoy, M., S. Erdem, Erdogan, G., et al. (1976) "Combination of genetic factors and chronic exposure to benzene in the aetiology of leukaemia." *Hum Hered.* 26:149-153.

3. Court of Common Pleas of Allegheny County, Pennsylvania. *Re: Toxic Substance Cases, Incorporated by reference: A. John Vogelsberger and Freda M. Vogelsberger vs. Owens-Illinois, Inc., et al.* Administrative Docket No. A.D. 03-319.