Business Bias:

How Epidemiologic Studies May Underestimate or Fail to Detect Increased Risks of Cancer and Other Diseases

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In spite of claiming primary prevention as their aim, studies of potential occupational and environmental health hazards that are funded either directly or indirectly by industry are likely to have negative results. The authors present three common scenarios in which faulty design of epidemiologic studies skews results, and list 15 study design flaws that lead to results that are dangerously misleading with regard to both the evaluation and the improvement of public health. *Key words*: epidemiology; industry influence; study design; public health.

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Interests other than those concerned with the protection of public health—in particular, personal ambition or economic profit—can heavily affect biomedical research,[1] and cancer research in particular.[2–5] There is ample evidence that, in spite of claiming primary prevention as their aim, occupational and environmental studies that are directly or indirectly sponsored by multinational corporations almost invariably lead to negative results.[6–8] In such studies the real risk of disease in subjects exposed to harmful factors is often underestimated. One way this is done is by indicating as safe environmental situations that very likely present risk. For example, in petrochemical and refinery-based epidemiologic studies conducted (or simply supported) by corporations, workers potentially exposed to about 50 substances classified as toxic, mutagenic, and carcinogenic[9] are regularly declared healthy.[10,11] There are several reasons to question these results.

Studying the scientific literature oriented to the identification of the disease risks in strategically and economically relevant activity sectors such as oil refineries and petrochemicals, it is common to observe a statistically significant reduction of the observed/expected ratio of cases (dead or ill) among exposed workers (vs unexposed). This may, of course, occur because there is no exposure at all, but in other instances the real cause of the negative results—that is, the absence of an association between exposure and adverse health effects—may reside in the epidemiologic study design.

We present three scenarios, examples of which have been observed in recent studies, in which real risks of disease are underestimated. In addition, we put forth 15 points, some of which are borrowed from a nearly 25-year-old analysis,[12] that are both critical and dangerously misleading with regard to both the evaluation and the improvement of public health. As reanalyses of specific data sets are not available, we cannot, however, make any direct evaluation or simulation of specific studies.

Scenario 1

If exposed and unexposed workers are not separated, the automatic and obvious consequence is a large underestimation of the real magnitude of risk among the exposed workers (misclassification error). This error might be negligible (statistically, not ethically, of course) only if and where the proportion of unexposed workers is not relevant (in terms of size, person-years, etc.). Only the classification of the whole cohort in the homogeneous subgroups of workers, therefore, will permit an estimate of the real risk magnitude.[13]

Scenario 2

A more serious misclassification bias occurs when exposed diseased workers are classified as unexposed controls.[14] This is often the case in studies of U.S. refinery workers, among whom the most heavily exposed workers are often "contract workers" who may work at a refinery or refineries cleaning tanks or installing insulation but who are not regular "employees" of the refinery. This "problem" has been known to the American Petroleum Institute (API) for more than 40 years. In 1958, the American Petroleum Institute (API) contracted with Dr. Robert Kehoe to design "An Epidemiologic Study of Cancer among Employees in the American Petroleum Industry."[14] In describing worker exposure classification Kehoe noted:

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> It was quickly discovered as various industrial situations were studied also that job titles differed greatly from company to company and indicated little if any relationship to the degree and kind of hazard. Men charged with the actual operation of the equipment, for example in the petroleum industry, may have very little or no contact with either petroleum or the various refined products, but the samplers and maintenance personnel may have frequent and heavy exposures. At the same time, maintenance and labor classifications may work in all parts of the refinery or, equally common, be assigned for a significant period of time to a single area. In reviewing the effect of technical changes in the refining processes on the exposure factor, one is immediately impressed by the fact that this is an extraordinarily fluid and dynamic industry. New processes evolve constantly, and this has been particularly true in recent years as companies moved rapidly from 'batch' type of operations to essentially 'assembly line' procedures. With this evolution, the degree and kind of contact change markedly. Maintenance problems are reduced and even presently widely-spaced 'turn arounds' are being substantially subcontracted by many companies. [It must be admitted that, although this development may diminish the exposure hazard for the refinery worker, it may be concentrating and augmenting the danger to the employees of companies specializing in this service-type operation.]
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> Consequently, even if accurate and reliable occupational records were obtainable, the local situations are constantly changing and improving so that the exposures of today are much less than those ten years past, and it can be predicted confidently that they are probably much greater than those of ten years hence.

Unfortunately, instead of trying to correct this problem, API-funded researchers have capitalized on this phenomenon to generate study findings that appear to show that workers potentially exposed to all kinds of known carcinogens and other toxins live longer than unexposed population controls. This is in part due to the fact that exposed contract workers with disease are moved from the exposed diseased category (the "a" box) to the unexposed disease category. For example, Otto Wong stated that a contract worker with leukemia (a plaintiff in a lawsuit against Mobil) who worked at a Mobil facility cleaning reactor vessels but did not work as a regular employee for Mobil would not be categorized as a Mobil worker. On the other hand, Wong stated that a Mobil lawyer whose office was located at the same facility would be included in the exposed group.[15]

For rare diseases, such non-random misclassification that switches exposed–diseased workers to the unexposed–disease category can easily produce results that show that "exposure" is protective. This is in fact what Wong has often found.[16]

Scenario 3

If we compare illness frequencies among exposed workers with those in the general population (which is normally less healthy than the workers when hired and even later) we create a "healthy-worker effect" (HWE) with the consequent related comparison bias. The HWE is too often considered inevitable. As a matter of fact, it is not only an *effect*, a *bias*, or finally, an epidemiologic *artefact*, but a serious error that can be avoided by an epidemiologic study design in which an internal comparison between exposed and unexposed workers is performed correctly. As a matter of fact, an unexposed group of oil refinery workers is often readily identifiable within the plant under study.

When two of these errors occur at the same time, a "negative" result is practically certain: a protective effect will be demonstrated, and the studied workers will show a reduction of their risk with a lower-than-expected number of observed cases (dead or ill).

In addition, the reduction of this risk might also be statistically significant when the 90% confidence interval (CI)—instead of the conventional 95% CI—is calculated around the point estimate (i.e., RR, SIR, SMR). In fact, the conventional 95% interval might not show any significant reduction due to its larger interval.

When we asked why this questionable methodologic approach is used, we received different answers: the data were analyzed in many ways (and that is often true); this way of analysis is usual (and again, this is often true); other approaches were not available; and, hard to believe, a different approach would be too costly.

In the light of such premises, we have identified 15 elements that, when present in epidemiologic studies, may lead to falsely negative results.[12] These elements do not meet the criteria for good epidemiologic practice oriented to the improvement of public health.

CRITICAL POINTS (ERRORS TO BE AVOIDED)

1. Privilege the use of descriptive instead of analytic statistics, and the adoption of cross-sectional instead of longitudinal epidemiologic studies;
2. fail to study the single homogeneous subgroups of workers (in terms of exposure);
3. consider only the exposure to one single substance, ignoring the possibility of exposure to multiple substances and their interaction;
4. keep the unexposed and exposed workers mixed (creating a dilution effect);
5. compare the exposed workers, who are usually selected according to their overall positive health condition, with the general population (instead of unexposed workers), creating a healthy-worker effect (and comparison bias);

6. take into consideration only one single disease (or disease family, e.g., cancers) rather than all diseases;
7. maintain disaggregation of homogeneous pathologies, thus making statistical significance more difficult to achieve;
8. fail to study reversible symptoms or serious sentinel abnormalities;
9. study neoplastic effects (usually having medium-long latency periods) at follow-up periods too short to allow for their development;
10. compare effects on the same target organ between groups of individuals exposed to different agents (e.g., asbestos workers vs tobacco smokers) having the same target (e.g., lung);
11. interpret the absence (or inadequacy) of both environmental (and biological) monitoring and epidemiologic studies as evidence of absence of exposure and negative health effects;
12. keep the measurements of exposures separated from the measurements of health effects;
13. privilege statistical significance rather than biological significance, and consider the results of large and multicentric studies more important than other factors (biology, exposure, etc.);
14. use the conventional two-sided statistical test instead of the one-sided statistical test, which appears to provide the greatest reassurance against missing an exposure-related effect[17]; and, last but not least,
15. use univariate analysis instead of a multivariate analysis that permits the simultaneous study of all the relevant variables (e.g., age at hire, sex, area, job, calendar period, length of employment, latency, etc.).

CONCLUSIONS

The scientific evidence currently available suggests that epidemiologic studies addressing the identification of health risks for workers occupationally exposed to noxious agents, as well as for residents in polluted areas, rarely fulfill the standards of scientific rigor and commitment to the principles of public health protection if they are sponsored by strong economic interests. For instance, studies of workers in oil refineries conducted with total economic independence have identified possible environmental and health risks associated with exposures to more than 50 substances classified as toxic, mutagenic, and carcinogenic, such as asbestos, arsenic, benzene, chromium, nickel, polycyclic hydrocarbons, and silica. The IARC has therefore evaluated exposures in oil refineries as probably carcinogenic to humans.[9] By contrast, other studies undertaken within the same areas of industrial production, supported by industry and of doubtful independence, do not report the existence of any risks.[6,10,11,15]

Epidemiologic investigations on oil refinery workers carried out in Liguria (Italy) have identified specific asbestos-related tumors, such as pleural[18,19] and lung[13] tumors, a finding that was subsequently and independently confirmed in Canada.[20] These findings were initially ignored and/or openly disputed, but were later accepted.[15] Only Kaplan[21] had previously registered an excess of mesotheliomas in these workers.

A review of studies of effects of exposures to selected chemicals (alachlor, atrazine, formaldehyde, and perchloroethylene) shows that 60% of such studies conducted by non-industry researchers found these chemicals hazardous, while only 14% of industry-sponsored studies did so.[5,22] There is a legitimate doubt that at least part of these studies effectively pursued the actual identification of specific risks, or complied with rigorous scientific criteria. Such studies have contributed to a harmful delay in the adoption of preventive measures and have downplayed the significance of primary prevention, especially in developing countries.[23]

The power of the limited number of multinational corporations is proven by the fact that they operate worldwide, with over 700 petroleum refineries where they employ about 1,200,000 workers. Additional workers are employed in related industries, where about 2,500 different products such as lubricants, bitumen (residual oils), fuels, solvents, fabrics, plastics, disinfectants, perfumes, etc., are produced.[24] Most studies sponsored by the companies owning the refineries have provided *reassuring* results.[6,15] Given the way in which the data were assembled and analyzed, however, they are definitely not reassuring.[7]

Based on this background, there is an urgent need for strengthening economically and intellectually independent scientific research that is explicitly oriented toward primary prevention (i.e., the protection of public health) and free from any business bias or bias due to any vested economic interest. We suggest, therefore, that qualified independent scientists be allowed to reanalyze the original data sets of studies that either 1) have been conducted or supported by sponsors having strong conflicting economic interests or 2) report negative results or a protective effect where there is a reasonable suspicion (a priori or suggested by other studies) of the presence of increased risk of an adverse health effect.

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