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cc: R. R. Cook
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SUBJECT: ALBERTA AMBIENT AIR STANDARDS FOR VINYL CHLORIDE

I have reviewed the two articles you provided that form the basis for Alberta's assessment of ambient air standards for vinyl chloride [(Falk et al.(1981)) and Kuzamack and McCaughy (1975)].

The Falk et al. article appears to be a well-balanced account of the epidemiology of hepatic angiosarcoma (HAS) in the United States. What is lacking is an assessment of VCM exposure intensities associated with VCM induced cases of HAS. Furthermore, there is no indication of whether or not HAS cases were associated with proximity to VCM emission sources. Apparently this was not the case, since it would have been pertinent to report such an association. A cautionary note was sounded in that for thorotrast-induced HAS cases, lower exposure was associated with longer latency. However unlike VCM, thorotrast is persistent in the body. I have enclosed a similar article on the epidemiology of HAS in Great Britain (Baxter et al.). That study did not include controls when assessing risk factors, used occupation

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as shown on the death certificates rather than as obtained through interview and therefore is a much less reliable assessment of HAS epidemiology. Even so, there is only the possibility of one case linked to geographic proximity to a PVC facility (no risk ratio provided) and several possible cases linked to low level VCM exposure at work.

The following are areas of difficulty I see with the Kuzamack paper:

(1) assessment of the consistency of the animal risk assessment models with human epidemiologic data across the dose-response curve,

(2) the problem of discrimination between the alternative mathematical models (e.g., linear versus probit) based on existing data,

(3) consistency of the mathematical models with biologic knowledge (e.g., knowledge about the metabolic activation requirements of VCM),

(4) the assertion that HAS accounts for only one half the VCM induced cancers and,

(5) applicability of the United States risk assessment to a situation in which the potential target population is much smaller.

The validity of the extrapolation of rat data to humans (Kuzamack and McCaughy) is based on crude estimates of HAS risk from existing positive human occupational studies of highly-exposed VCM employees. Clearly, there is a correspondence in that both man and rodents evidence increased HAS risk with exposure. The validation, however, is performed at only one point on the dose-response curve, and therefore, does not validate the correspondence at lower exposures (see Gehring et al. article for an alternative approach to the extrapolation issue). There are now much more extensive human data than were available either to Kuzamack and McCaughy or Gehring et al.

Internationally, the number of VCM-related cases now exceeds 100. What has been remarkable is that most of the cases worked as autoclave cleaners at one time or another and that cases tended to cluster in certain plants. This would suggest that higher TWA exposures were experienced by the cases than the 350 ppm TWA assumed by Kuzamack and McCaughy.

It may also be that there is a steep slope in the dose-response curve. The issue facing the Alberta government is that of the nature of the dose-response curve at very low exposure intensities. Currently, there is no evidence in man that exposures below 1 ppm lead to HAS cases. Gehring et al. have shown that the number of predicted cases based on extrapolation to low level

exposure depends greatly on the model assumed (e.g., linear versus probit). Unfortunately, it is difficult to distinguish between alternative models based on experimental data because sample sizes at low doses may be inadequate. The only test of a model model can come from a comparison of predictions with actual human experience at lower exposure intensities. This has not been formally done to my knowledge.

I have included articles by Tamburro, Watanabe et al., and Guengerich and Watanabe concerning the mechanism of action of VCM. It is evident that metabolic activation plays a role and that alternative metabolic pathways are available. The mathematical models proposed by Kuzamack and McCaughy simply do not consider these biologic issues.

Recent articles by Theriault do not support the contention HAS accounts for only one half of the cancers induced by VCM.

An important component of risk assessment is knowing the size of the population possibly at risk. In the United States, this was estimated to be in excess of 4 million people within a 5 mile radius of VCM or PVC plants. The number of people possibly at risk in Alberta must be much smaller than 4 million. This should be considered in the risk assessment.

In summary, to my knowledge, epidemiologic evidence that people exposed to less than 1 ppm VCM are at increased risk of

developing HAS is lacking. Yet because of the signal tumor nature of HAS, such evidence would be relatively easy to develop. The regulatory actions are being contemplated based on extrapolation of animal data via mathematical models to low level exposures rather than based on direct human evidence. While the objective is clearly to prevent any cases of VCM-induced HAS from occurring, it is unclear whether or not a more stringent ambient air standard will impact on the likelihood of such cases.

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