UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
RESEARCH AND DEVELOPMENT

MEMORANDUM

SUBJECT: Correcting Methylene Chloride Risk Estimates for Pharmacokinetic Dose-Rate Effects

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This memorandum describes the development of a set of "dose-rate correction factors" to be used when calculating cancer risk estimates for inhalation of methylene chloride. The correction reflects the changes in the degree of metabolic activation of methylene chloride into the presumed proximate carcinogen as a function of different vapor concentrations and durations of exposure. As a result, short but intense exposures lead to greater "toxicologically effective" or "delivered" doses at the tissue site of toxic action than the degree of exposure would indicate. In such cases, use of an incremental unit risk expressed in units of vapor concentration will indicate less risk than the intended extrapolation based on delivered dose.

Background

As part of the chlorinated solvents effort, EPA has recently revised its risk assessment for methylene chloride (USEPA 1987a, referred to below as the "Update"). The newly calculated unit risk of 4.7×10^{-7} per ug/m^3 is based on consideration of the pharmacokinetics of methylene chloride. The extrapolation of risk across species and across doses is now done on the basis of relative levels of metabolically activated compound at the

presumed site of toxic action (the "delivered dose"), rather than on externally applied exposure to methylene chloride itself. These delivered doses are estimated using a physiologically-based pharmacokinetic model, as described in the Update.

Although risk is being figured on the basis of delivered dose, it is impractical to estimate the delivered dose for every human exposure of interest. For convenience of use, the unit risk is expressed in terms of the vapor concentration in the ambient air being breathed; i.e., the unit risk of 4.7×10^{-7} per ug/m^3 is the estimated risk based on the delivered dose that follows continuous exposure to 1 ug/m^3 of vapor in the ambient air. (The Update may be consulted for details of this calculation.) The use of a unit risk for estimation of cancer risks rests on the assumption that, at least at low doses, risk is directly proportional to the degree of exposure. The unit risk is the low-dose slope of the dose-response curve (as determined by an upper bound linear extrapolation from bioassay data at higher doses), and represents an upper bound estimate of the increase in risk per unit of exposure. This curve is based on continuous exposure throughout life. When risks for episodic bouts of inhalation are being calculated, it is assumed that the risk from a bout is equivalent to that of a lifelong exposure to the low concentration that yields the same total ppm-hours of exposure (the so-called lifetime average daily equivalent, or LADE). In other words, the assumption is that toxic effect is proportional to the total cumulative lifetime exposure, regardless of the rate at which it is experienced.

This assumption--that there are no dose-rate effects--can be divided into two parts: (a) that the time pattern of inhalation exposure does not affect the fraction of the compound that is delivered to the site of toxic action as metabolically activated carcinogen; and (b) that the time pattern of target-tissue exposure to such activated compound does not affect the degree of toxic response, which only depends on the cumulative amount of such exposure. It is important to note that the correction factor discussed in this document addresses only the first issue, which is in the realm of pharmacokinetics. The second issue is a question of how the actual mechanism of toxic action operates, and is beyond the scope of the present analysis. Until we have a means of addressing the dependence of toxic reaction on the time pattern of dose delivery, the second part of the assumption--that all exposures resulting in the same cumulative delivered dose have equal probabilities of tumorigenic response--must be retained.

To the degree that delivered doses vary in direct proportion to the magnitude of external exposure, the use of the unit risk will correctly reflect the underlying delivered dose basis of risk estimation. This is generally the case for low exposure levels. In the case of methylene chloride, however, there is

pharmacokinetic evidence that this assumption does not hold at higher vapor concentrations; a key pathway of metabolic detoxification has limited capacity, and at higher exposure levels the degree of metabolic activation of methylene chloride (by another, non-saturable pathway) is consequently proportionally greater than at lower exposures. This can lead to pharmacokinetic dose-rate effects--short but intense exposures lead to proportionally greater "delivered" doses at the tissue site of toxic action than the cumulative external exposure would indicate. In such cases, use of the unit risk will imply less risk than the intended extrapolation based on delivered dose. Risk calculation using the unit risk requires a correction to account for the greater degree of metabolic activation occurring when exposures consist of episodes of breathing high concentrations.

The magnitude of the correction, then, will be the ratio of the delivered dose under the actual conditions of exposure (high concentration for a short time) to the delivered dose that is presumed by using the unit risk, i.e., one that maintains the proportionality to external concentration characteristic of low doses. The required correction will be different for every exposure scenario; it is not practical to recalculate it for every case. Instead, I will develop a matrix in which entries correspond to the correction applicable to various combinations of duration and level of exposure. The appropriate correction for a particular case can then be looked up. (This method is not applicable for exposures in which the air concentration varies markedly over the course of exposure, or for a series of episodes experienced in rapid succession, since these scenarios are not included in the matrix.)

Calculation

The pharmacokinetic model used in the calculations described here is the same as that described and used in the Update document, the human model of Andersen, et al. (1987). As in the Update, the breathing rate and cardiac output were modified to reflect EPA's standard assumptions about activity levels. I considered 240 distinct exposure scenarios, comprising sixteen different vapor concentrations, ranging from 10 ppm to 8000 ppm, for each of fifteen different exposure durations, ranging from one minute to 12 hours. A separate run of the pharmacokinetic model for each scenario was used to determine the estimated cumulative delivered doses (in units of mg-eq of metabolically activated compound produced per liter of tissue over the course of exposure) to both liver and lung tissue. For example, according to the model, a 15 minute exposure to 1000 ppm results in a total delivered dose to the liver of about 2.1 mg-eq per liter of tissue. (The tissue-level exposure continues past the termination of inhalation, until the accumulated burden of

compound in the body is eliminated. The model runs were for 48 hours to cover this post-exposure period.)

For each scenario, I also calculated the delivered dose assumption implicit in the use of the unit risk with cumulative lifetime exposure. First, a lifetime average daily equivalent (LADE) exposure concentration was calculated by prorating the episode of exposure over a full 70 year lifetime. For example, the LADE corresponding to a 15 minute exposure to 1000 ppm is the continuous lifetime exposure that results in the same total of 250 ppm-hours--in this case it is about 4.08×10^{-4} ppm, or 1.44 ug/m^3. If the proportionality between total delivered dose and total ppm-hours of exposure used in the unit risk is maintained at all exposure levels and dose rates, the 15 minute exposure to 1000 ppm and the lifelong exposure to 1.44 ug/m^3 should share a delivered dose that is 1.44 times that from a lifelong exposure to 1 ug/m^3 (the basis of the unit risk calculation), or about 0.73 mg-eq/L in the liver. Thus, using the unit risk to estimate the risk from the actual 15 minute exposure episode underestimates the cumulative effective dose to the liver (and by assumption, the lifetime risk of liver cancer) by about 2.1/0.73 = 2.9-fold.

A similar calculation for the lung yields a factor of 1.5-fold; the difference in the factor between tissues reflects differences in enzyme activities for the two principal biotransformation pathways. As described in the Update document, and in the accompanying technical document (USEPA 1987b), the overall unit risk is the sum of the organ-specific risks for liver and lung at one unit of exposure. The "corrected" overall unit risk will be the sum of the unit risks for the two organs, each corrected by its own factor. Thus, the correction factor to the overall unit risk is the weighted average of the organ-specific correction factors, with the weights being the organ-specific unit risks. The calculations in the Technical document (USEPA 1987b) show that the lung-specific unit risk accounts for 71.3% of the total, while the liver unit risk accounts for 28.7%. Thus, the magnitude of the lung correction factor predominates in the overall correction. The overall correction is, in this case, (.713)1.5 + (.287)2.9 = 1.9. That is, the risk calculated for a 15 minute exposure to 1000 ppm should be increased by 1.9-fold to account for the pharmacokinetic dose-rate effect. The estimated upper bound risk from one such episode is the product of the unit risk, the LADE, and the correction factor, or $(4.7 \times 10^{7}) \times (1.44) \times (1.9) = 1.3 \times 10^{-6}$.

A calculation similar to the one outlined above was carried out for each of the 240 exposure scenarios. The results are tabulated in a matrix of correction factors in Table 1. Examination of the matrix confirms that low exposure levels require no substantial correction, but the required factor grows with both vapor concentration and duration of exposure. The

Table 1.

Pharmacokinetic Dose-Rate Correction

Air Concentration

Duration	10 ppm	20 ppm	50 ppm	100 ppm	150 ppm	200 ppm	300 ppm	400 ppm	500 ppm	600 ppm	800 ppm	1000 ppm	2000 ppm	4000 ppm	6000 ppm	8000 ppm
1 min	1.0	1.0	1.0	1.0	1.0	1.1	1.1	1.1	1.1	1.1	1.2	1.2	1.4	1.6	1.6	1.7
2 min	1.0	1.0	1.0	1.0	1.1	1.1	1.1	1.2	1.2	1.3	1.3	1.4	1.5	1.7	1.8	1.9
5 min	1.0	1.0	1.0	1.1	1.1	1.2	1.3	1.3	1.4	1.4	1.5	1.5	1.8	2.0	2.1	2.2
10 min	1.0	1.0	1.1	1.1	1.2	1.2	1.3	1.4	1.5	1.5	1.7	1.7	2.0	2.2	2.3	2.4
15 min	1.0	1.0	1.1	1.2	1.3	1.3	1.5	1.6	1.6	1.7	1.8	1.8	2.2	2.4	2.5	2.6
20 min	1.0	1.0	1.1	1.2	1.2	1.3	1.5	1.6	1.7	1.7	1.8	1.9	2.2	2.4	2.5	2.6
30 min	1.0	1.1	1.1	1.2	1.3	1.4	1.6	1.7	1.8	1.9	2.0	2.1	2.3	2.5	2.7	2.7
45 min	1.0	1.1	1.1	1.2	1.4	1.5	1.7	1.8	1.9	2.0	2.1	2.2	2.5	2.6	2.7	2.8
1 hr	1.0	1.1	1.1	1.3	1.4	1.5	1.7	1.9	2.0	2.1	2.2	2.2	2.5	2.7	2.8	2.9
2 hr	1.0	1.1	1.1	1.3	1.5	1.6	1.9	2.0	2.1	2.2	2.3	2.4	2.6	2.9	3.0	3.0
3 hr	1.0	1.1	1.2	1.4	1.6	1.7	1.9	2.1	2.2	2.3	2.4	2.5	2.7	2.9	3.1	3.1
4 hr	1.0	1.1	1.2	1.4	1.6	1.8	2.0	2.2	2.3	2.4	2.5	2.6	2.8	3.0	3.1	3.2
6 hr	1.0	1.1	1.2	1.4	1.6	1.8	2.1	2.3	2.4	2.5	2.6	2.7	2.9	3.1	3.1	3.2
8 hr	1.0	1.1	1.2	1.4	1.7	1.9	2.2	2.3	2.4	2.5	2.6	2.7	3.0	3.1	3.2	3.2
12 hr	1.0	1.1	1.2	1.5	1.7	2.0	2.3	2.4	2.6	2.6	2.8	2.8	3.0	3.2	3.2	3.3

increments are closely enough spaced that factors for scenarios not listed can be obtained to a close approximation by choosing the nearest listed example. I would suggest rounding upward (to the next highest concentration and duration) to avoid under-correcting.

Figure 1 shows the magnitude of the factor plotted as a function of exposure duration for a number of vapor concentrations (i.e., columns of Table 1 are plotted). For very short exposures, even high vapor concentrations require only a small correction. Below 100 ppm or so the correction is never substantial, even for long exposures. At higher vapor concentrations, however, the correction factor can be substantial for all except the shortest exposures (less than 15 minutes). Figure 2 shows the factor plotted as a function of air concentration for various durations of exposure (i.e., the rows of Table 1 are plotted). The factor rises very rapidly with concentration, more so for longer durations, but then rises only gradually above 1000 ppm.

Discussion

There is experimental evidence for the saturation of the detoxification pathway, and consequent increase in metabolism by the putatively activating pathway, so the phenomenon outlined here has real existence. It should be borne in mind, however, that the magnitude of the pharmacokinetic dose-rate correction is calculated on the basis of a mathematical model of methylene chloride pharmacokinetics, rather than on any direct measurements. This model has been carefully examined in the Update and Technical Analysis documents cited above, but in many respects it lacks thorough validation. In particular, one might question the model's ability to accurately portray events on a very short time scale. For example, absorption of vapor from the lung air into the pulmonary blood supply is considered to be instantaneous. This simplification may be perfectly adequate for predicting events on moderate to long time scales, but the correction factor for one minute exposures may not be realistically represented. In sum, the calculations of correction factors reported herein are only as reliable as the model on which they are based, and the model has not been validated for such purposes. The correction factors are consequences of the representation of pharmacokinetics by the model, which representation is considered to be generally correct, but unverified in detail.

It should be made very clear that the term "dose-rate effect" is used in a limited sense in this document. The effect is a pharmacokinetic one--the dependence of the degree of metabolic activation of inhaled methylene chloride on the time pattern of its administration. Even after this effect is corrected for, it is still true that the delivered dose from the

Figure 1. Pharmacokinetic Dose-Rate Correction

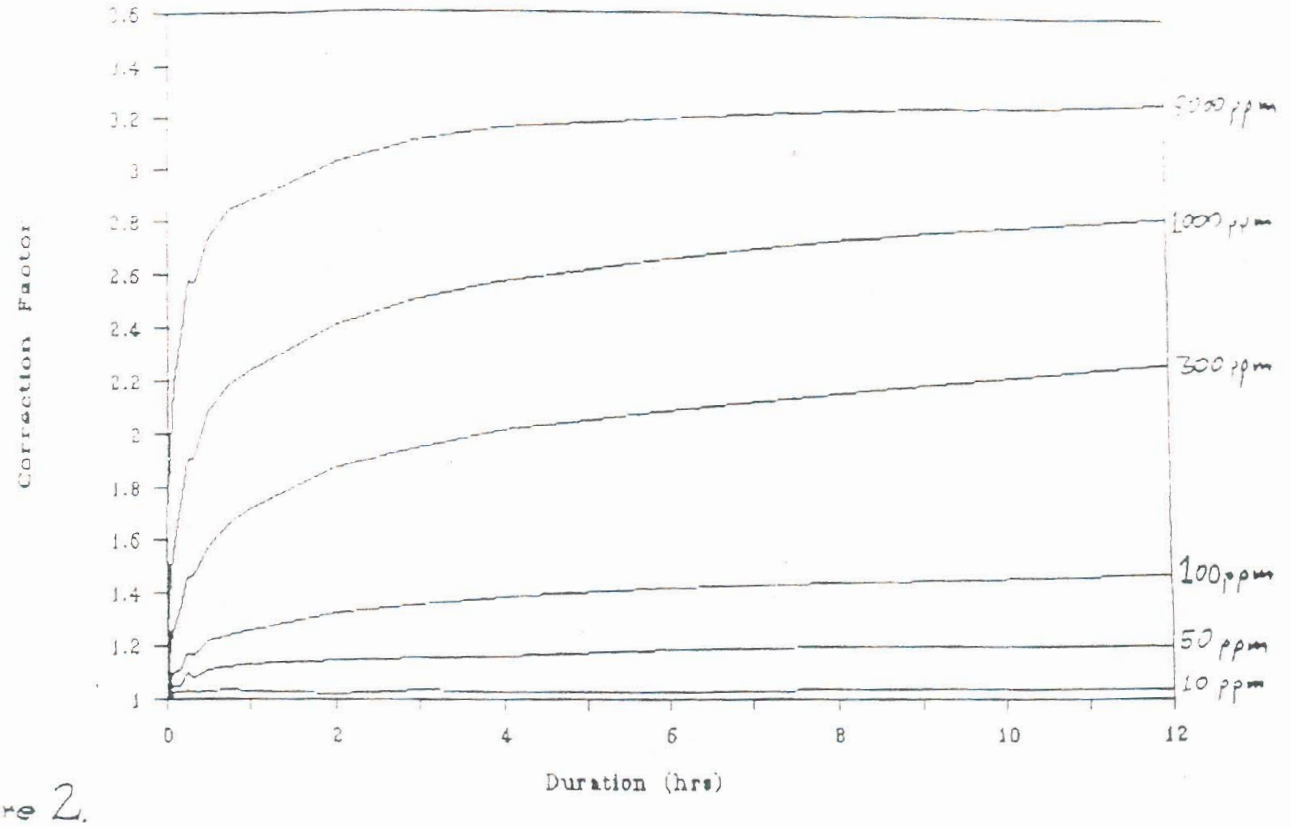
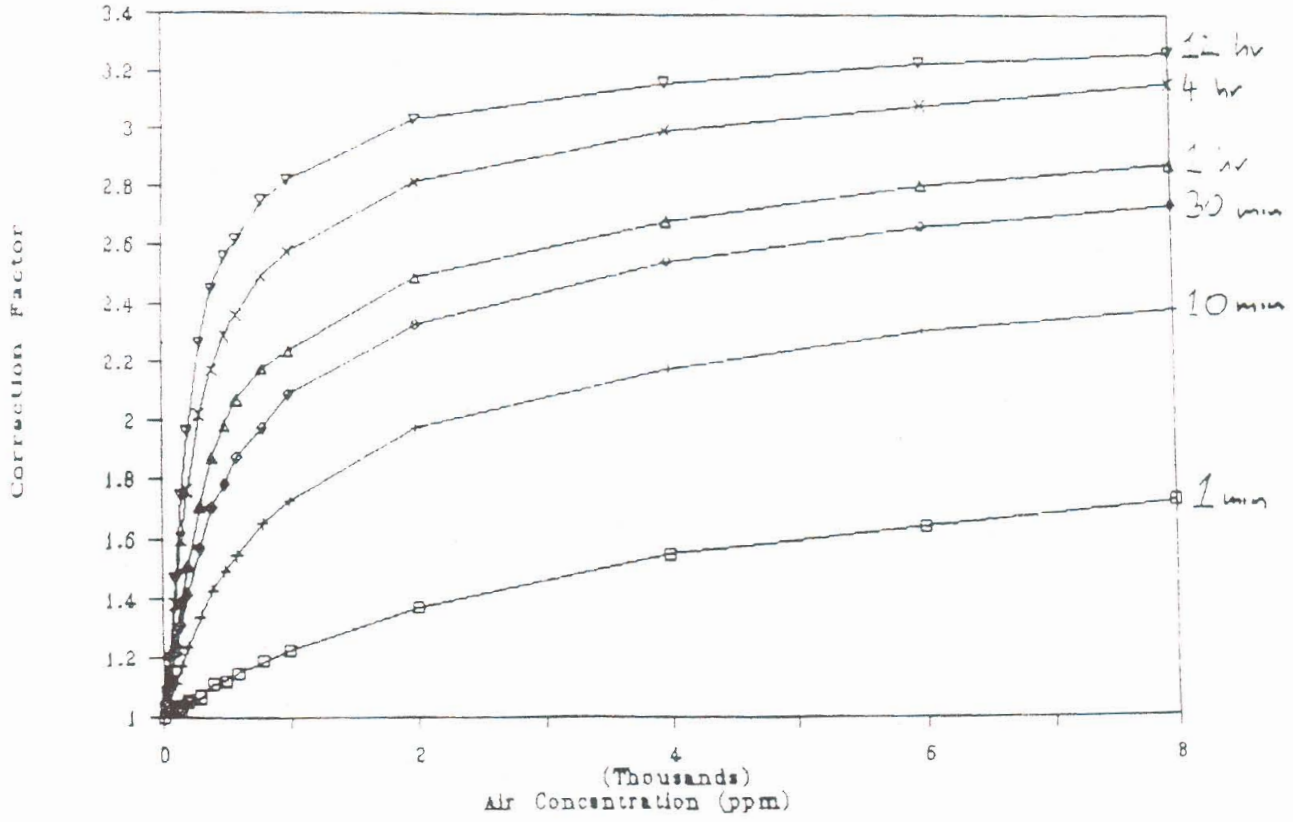


Figure 2.



short, intense exposure is experienced by the target tissue as a brief peak of metabolically activated compound, while a long-term exposure to a lower concentration results in a similarly long-term and low tissue exposure to the putative proximate carcinogen. This analysis corrects for only the total cumulative amount of such tissue-level exposure, but not its pattern of delivery over time. The analysis does not and cannot address the toxicological equivalence of these different patterns. The answer to that question depends on the biological mechanism of carcinogenic action and how it varies with the pattern of exposure to a given amount of proximate carcinogen. In other words, the assumption that only the concentration-time product matters, and not the dose-rate, is still used as far as the estimation of the risk engendered by the delivered dose is concerned; i.e., cumulative lifetime tissue-level exposures to metabolically activated carcinogen are assumed to be equal in tumorigenic effect. Likewise, basing low-dose risk estimates on the amount of activated carcinogen in the tissues does not mean that risk is truly proportional to these low delivered doses, even though we assume that it is for purposes of low-dose extrapolation. What has been done is essentially to measure dose at a more meaningful level--activated compound at the site of action--but assumptions about how to extrapolate risk across species, to low doses, and across time patterns of exposure, remain even for this more sophisticated dose measure.

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References

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