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A Method for Calculating the
Acceptable Daily Intakes (ADI's) for Man
of Volatile Extraction Solvents Using
Established Threshold Limit Values (TLV's)
For Inhaled Vapors

by

T. R. Torkelson, Sc.D.
Senior Research Toxicologist

Howard C. Spencer, Ph.D.
Research Scientist

Biochemical Research Laboratory
The Dow Chemical Company
Midland, Michigan 48640
U.S.A.

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Acceptable Daily Intakes (ADI's) for man in terms of mg/kg body-weight have been established by the Joint FAC/WHO Expert Committee on Food Additives for many of the well-known additives in common use. Similarly, Maximum Acceptable Daily Intakes in terms of mg/kg body-weight for pesticide residues have been established by the Joint Meeting of the FAO Working Party and the WHO Expert Committee on Pesticide Residues.

In general, long-term (two year) dietary feeding studies in laboratory animals furnish the basis of judgement in establishing an ADI. Relying solely on data obtained on laboratory animals, it is common practice to apply a 100-fold "safety" factor. In cases where data are available from experience with human subjects or from controlled human studies, which supplement and confirm the observations on animals, a smaller (10-fold) safety factor may be justified.

Pozzani et al¹ have shown a relationship between single dose inhalation data and single dose oral data for certain compounds; however, similar studies comparing repeated inhalation data and repeated oral data are not available. This is because meaningful, long-term dietary or water feeding data with volatile compounds are not obtainable due to the loss of the test compound from the food or water during the study, and because of decreased palatability due to taste and odor. Incubated doses or doses contained in capsules and fed orally are not representative of a dietary residue and place unduly high acute toxicity stress on the animal at the time of dosing or when the capsule dissolves in the alimentary tract. Due in part to these technical difficulties, no

chronic (2 year) dietary feeding studies have been carried out with the common extraction solvents: ethylene dichloride, $\text{CH}_2\text{Cl}-\text{CH}_2\text{Cl}$; methylene chloride, CH_2Cl_2 ; and trichloroethylene, $\text{CHCl}=\text{CCl}_2$.

In order to surmount these technical difficulties, the following alternative method is suggested.

Industrial experience has shown that certain levels of commonly used solvents can be inhaled safely by workmen who are exposed 7 or 8 hours daily for their working lifetime. These acceptable, safe concentrations have taken various names such as Hygienic Standards, Maximum Allowable Concentrations, Maximum Acceptable Concentrations and MAK's. Perhaps the oldest, and best documented are those used in the United States which are called Threshold Limit Values (TLV's).² Threshold Limit Values (TLV's) are reviewed and issued annually by a committee of the American Conference of Governmental Hygienists (ACGIH).² A TLV is defined by the ACGIH as follows:

Threshold limit values refer to airborne concentrations of substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse effect. Because of wide variation in individual susceptibility, however, a small percentage of workers may experience discomfort from some substances at concentrations at or below the threshold limit, a smaller percentage may be affected more seriously by aggravation of a pre-existing condition or by development of an occupational illness.²

According to Stokinger and Woodward³:

These threshold limit values represent a maximal average concentration of a substance in workroom air that provides no hazard to health or well-being of the worker during his working lifetime. Tested under practical conditions over a period of years, these values have considerable validity. Most have safety factors incorporated which are often of appreciable magnitude. Some of these arise because the values are based on considerations other than health--such as freedom from irritation; others, because of engineering adaptability, may provide large factors of safety to health.

Use experience has borne out the fact that if the average exposure of the workmen does not exceed the TLV there is little likelihood of injury. The basis for selection of the TLV's are diverse and include such criteria as objectionable odor, eye irritation, anesthesia, as well as systemic injury. Documentation to support the safe use of specific TLV's are published by the ACGIH.⁴ For the three volatile extraction solvents discussed in this paper, references 5 through 9 are particularly pertinent. Threshold Limit Values have been established as legal safety requirements for obtaining U.S. Federal Supply Contracts.¹⁰

The American National Standards Institute Incorporated (ANSI) has published consensus standards for safe repeated exposure to these extraction solvents Z37.21-1969; Z37.23-1969; Z37.19-1967.^{11, 12, 13} This committee composed of representatives of

Labor, Government, Universities, Industry, Military and other groups has adopted maximum average figures identical to the TLV's recommended by the ACGIH for these extraction solvents.

Obviously if the TLV is based on odor, discomfort, or respiratory irritation, the TLV bears little relationship to an ingested dose; but for ethylene dichloride and trichloroethylene the criteria used in establishing the TLV's for inhaled vapors are based primarily on systemic toxicity. For methylene chloride the TLV has been selected to prevent anesthetic changes; since organic injury has been shown not to occur from repeated exposure of animals to 10 times the TLV, an additional 10-fold safety factor results.⁵

Consequently, for these volatile extraction solvents, it is valid to use the Threshold Limit Values (TLV's) in terms of mg/m^3 of air as a basis for calculating the Acceptable Daily Intakes (ADI's) in terms of mg/kg body-weight. Similar calculations have been used to establish drinking water standards by Stokinger and Woodward.³ The following is duplicated from their publication:

TABLE 3
Limits for Organic Substances in Water Calculated From Threshold Limits for Air*

Organic Compound	Absorption Factor		Limit for Water ppm	Threshold Limit for Air $\text{mg}/\text{cu m}$
	Inhalation	Ingestion		
Acetone	0.5	1.0	6,000	1,000
Acrylonitrile	0.75	0.85	240	20
Allyl alcohol	0.75	0.8	55	5
Aniline	0.5	1.0	47	5
Benzene	0.35	0.4	340	25
Carbon tetrachloride	0.3	0.5	480	25
Ethylenediamine	0.75	0.8	140	10
Formaldehyde	0.8	0.8	30	5
Methyl bromide	0.4	0.5	240	10
Methylchloroform	0.1	0.5	2,700	500
Phenol	1.0	1.0	95	5
Pyridine	0.1	0.5	30	10

* All figures approximate.

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In the conversion of the amount of volatile solvent in the form of vapor absorbed by the lungs into an equivalent amount of solvent ingested, certain factors and assumptions are required.

1. The volume of air that a human breathes is related to the amount of solvent sorbed by the lungs. On the basis of the generally accepted work of Silverman et al,¹⁴ it is assumed that moderately active workmen will inhale about 10 cubic meters (m^3) of air per 8 hour workday. This is the same factor used by Stokinger and Woodward.³
2. Less than 100% of the solvent in the air breathed in by humans is sorbed through the lungs. Stokinger and Woodward³ suggest 75% but McCollister et al,¹⁵ in a study using monkeys, found that an average of only 30% of the total amount of inhaled carbon tetrachloride was absorbed. Carbon tetrachloride is less water soluble, less sorbed, and probably less retained than the solvents under consideration here. The smaller the lung retention factor used in calculating the daily retained dose, the smaller the calculated daily sorbed dose, and therefore, the greater the safety factor in converting to daily ingested dose. In the absence of other data, the most conservative position is assumed. Therefore, the lowest probable retention factor for these solvents, based on carbon tetrachloride at 30%, is used in all calculations instead of the less conservative 75% suggested by Stokinger and Woodward.³

Using these factors and assumptions, the calculation of the Acceptable Daily Intake (ADI) in terms of mg/kg body-weight for these volatile solvents may be made as follows:

$$\frac{\text{TLV}(\text{mg}/\text{m}^3\text{air}) \times 10(\text{m}^3\text{air}) \times 0.3(30\% \text{ retention})}{60(\text{kg, avg. body wt.}) \times 10(\text{added safety factor})} = \text{ADI}(\text{mg}/\text{kg body-wt})$$

Thus, the Acceptable Daily Intakes (ADI's) for these three volatile extraction solvents may be calculated:

ETHYLENE DICHLORIDE

$$\frac{200 * x 10 \times 0.3}{60 \times 10} = 1.0 \text{ mg/kg body-weight}$$

METHYLENE CHLORIDE

$$\frac{1740 * x 10 \times 0.3}{60 \times 10} = 8.7 \text{ mg/kg body-weight}$$

TRICHLOROETHYLENE

$$\frac{535 * x 10 \times 0.3}{60 \times 10} = 2.7 \text{ mg/kg body-weight}$$

Conclusions

Considerable difficulty has been encountered in obtaining meaningful long-term feeding data on laboratory animals using volatile solvents. It is recommended that the Threshold Limit Values (TLV's), established on the basis of vapor toxicity data on animals and confirmed through human tests and experience, be employed to calculate the Acceptable Daily Intakes (ADI's) for man. These ADI's can then be used in the accepted manner to establish residue tolerances for these volatile extraction solvents in food.

*Threshold Limit Values (TLV) as published by the American Conference of Governmental Industrial Hygienists (ACGIH) (1969).

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