Correlation of Lethal Doses of Industrial Chemicals between Oral or Intraperitoneal Administration and Inhalation Exposure#

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Abstract: Correlations of lethal doses of industrial chemicals between oral or intraperitoneal administration and inhalation exposure in rats and mice were investigated. LC$_{50}$ values for inhalation exposure and LD$_{50}$ values for oral and intraperitoneal administration were obtained from the Registry of Toxic Effects of Chemical Substances. LC$_{50}$ and LD$_{50}$ values were plotted on ordinate and abscissa, respectively, using logarithmic scales. A correlation coefficient of $r=0.624$ ($n=146, p<0.001$) was obtained for LC$_{50}$ (ppm) and LD$_{50}$ (mg/kg) values with oral administration (oral LD$_{50}$) in rats. This correlation was improved by converting the units of LC$_{50}$ from ppm to ppm h (cumulative dose), and by converting the units of LD$_{50}$ from mg/kg to mmol/kg. The correlation coefficient was $r=0.742$ when ppm*hr and mmol/kg were adopted for LC$_{50}$ and LD$_{50}$, respectively. A similar improvement in correlation coefficients by the same unit conversion was also observed between LC$_{50}$ and LD$_{50}$ with intraperitoneal (i.p.) administration (i.p. LD$_{50}$) in rats. Correlations between LC$_{50}$ and oral LD$_{50}$ in mice were also improved by the same unit conversion. The correlations between LC$_{50}$ and i.p. LD$_{50}$ were higher than those between LC$_{50}$ and oral LD$_{50}$ both in rats and mice. In these correlations, coefficients obtained in rats were greater than corresponding coefficients in mice. We calculated equations to estimate LC$_{50}$ values accompanied by confidence limits from oral or i.p. LD$_{50}$ values.

Key words: LC$_{50}$, LD$_{50}$, Correlation coefficients, Chemicals, Rats, Mice

Introduction

There is a large body of toxicity data for industrial chemicals. In many reports, toxic doses are obtained by administration via the oral or intraperitoneal routes. However, many volatile chemicals are taken into body by inhalation in normal living and occupational circumstances, and there is a need for toxic doses to also be obtained in inhalation experiments. Inhalation exposure experiments are difficult to do because the installation of exposure apparatus is very expensive and running costs are high. For such reasons, most toxic doses are obtained by oral or intraperitoneal, or in some cases subcutaneous or intravenous administration. At present, the human risk due to exposure to chemicals is calculated based upon many assumptions in order to extrapolate animal data to humans.$^{1,2}$ An extrapolation of data obtained by injection routes to inhalation exposure is involved in these assumptions. If we are able to estimate toxic doses in inhalation exposure from data in oral or other injection routes, risk assessment becomes more reliable. In this study, therefore, we calculated the degree of correlation between toxic doses calculated in inhalation exposure and in injection experiments$^{3}$. In general, the toxic action of chemicals is not as specific as that of pharmaceutical drugs or pesticides. For example, lead is neurotoxic due to a direct effect of lead on nerve cells. On the other hand, severe anemia is elicited in lead intoxication.
Lead inhibits hemoglobin synthesis at very low blood concentrations. These facts indicate that lead possesses at least two sites of action. Among organic solvents, carbon disulfide causes disorders of the central and peripheral nervous system, in addition to renal dysfunction and hypertension. These examples show that the toxic dose level depends on its site of action and that a toxic dose is not always definitive. Among different toxic doses, the lethal dose seems to be almost the only parameter which can be determined clearly. Therefore, we adopted lethal doses to represent the toxic dose of chemicals. Lethality data were collected from the Registry of Toxic Effects of Chemical Substances (RTECS) because we needed a large number of lethal doses to perform statistical treatment. We calculated correlation coefficients between LC50 values in inhalation exposure and LD50 values in oral or intraperitoneal administration.

Materials and Methods

We selected all compounds for which the LC50 values and exposure time were described in the RTECS, 1995 version. Compounds that were solid at room temperature were not included. Compounds for which the LD50 values by oral or intraperitoneal administration (oral LD50 or i.p. LD50) were given in the RTECS were included in this study. LD50 values by other injection routes were not utilized because the sample sizes in subcutaneous or intravenous administration were small. Animal species were limited to rats and mice because the sample sizes of other animals were very small. Statistical treatment of LC50 and LD50 values for the calculation of correlation coefficient was performed on a PC using SPSS 6.1 for Windows software which was purchased from SPSS Japan Inc.

Results

The LC50 values for inhalation exposure and oral or i.p. LD50 values in rats or mice were plotted for many chemicals. In Fig. 1, the inhalation LC50 values and the oral LD50 values in rats were plotted for 146 chemicals on the ordinate and abscissa, respectively. A logarithmic scale was used for both the ordinate and abscissa. In Fig. 1A, LC50’s were expressed in ppm. Exposure duration in LC50 data obtained from RTECS was not considered. LD50 values were expressed as mg/kg because all of LD50 data in RTECS was given as mg/kg or µg/kg. The correlation coefficient between these two parameters was calculated to be r=0.624 (n=146, p<0.001) (Table 1). In Fig. 1B, the units for LD50 were converted from mg/kg to mmol/kg, and the units for LC50 remained as ppm. From the relationship in Fig. 1B, r=0.684 was obtained. As can be seen in this coefficient, the correlation was improved by converting the units for LD50 from mg/kg to mmol/kg. In Fig. 1C, ppm h (multiplication of LC50 in ppm and exposure duration in hr obtained from RTECS data) was used instead of ppm as the units for LC50. The units for LD50 were kept as mg/kg, and a value of r=0.681 was obtained. As Fig. 1C shows, the correlation was improved compared to Fig. 1A, by using cumulative exposure concentration (ppm h). The LC50 and LD50 values in Fig. 1D are expressed as ppm h and mmol/kg, respectively. The correlation coefficient in Fig. 1D, r=0.742, was greater than those in Fig. 1B and in Fig. 1C.

The same procedure was applied for the calculation of the correlation coefficients between LC50 values and i.p. LD50 values in rats (n=64). The units in Figs. 2A, 2B, 2C, and 2D correspond to those in Figs. 1A, 1B, 1C, and 1D, respectively. The correlation coefficients in Figs. 2A and 2B are 0.777 and 0.797, respectively (Table 1). As these coefficients show, the correlation was improved by converting the LD50 units from mg/kg to mmol/kg. The other coefficient, 0.867, was obtained in Fig. 2C, in which the LC50 units, ppm, was replaced with ppm h. The LD50 was expressed as mg/kg, and the correlation was greatly improved compared to Fig. 2A. In Fig. 2D, a coefficient of 0.895 was obtained, which was greater than those obtained in Figs. 2B and 2C. Also in the relationship between LC50 and i.p. LD50 values, the correlation was improved by replacing the LD50 units of mg/kg with mmol/kg, and the LC50 units of ppm with ppm h. LC50 and LD50 values obtained in mice were plotted in the same way as done in rats. LC50 and oral LD50 values in mice were plotted in Figs. 3A, 3B, 3C, and 3D, each unit of which corresponds to that in Figs. 1A, 1B, 1C, and 1D, respectively. In these relationships between LC50’s and i.p. LD50’s, there was an improved correlation by converting the unit of mg/kg to mmol/kg. However, there was no improvement in this correlation with conversion of the unit of ppm to ppm h (Table 1).

For each linear regression, the following equation was considered.

\[ \log_{10} Y = a \cdot \log_{10} X + b \]  

(A)
Fig. 1. Correlation of LC₅₀ values in inhalation exposure and LD₅₀ values in oral administration in rats
Units of ordinate and abscissa are as follows: ppm and mg/kg in Fig. 1A (upper left), ppm and mmol/kg in Fig. 1B (upper right), ppm h and mg/kg in Fig. 1C (lower left), and ppm h and mmol/kg in Fig. 1D (lower right). Regression line (solid line), 95% confidence limits for the regression line (broken), and 95% confidence limits for individual values (dotted) were calculated.
From equation (A), the following equation (B) can be derived.

\[ Y = X^a \cdot 10^b \]  

Parameters, \( a \) and \( b \), were calculated from the linear regression. All these results are summarized in Table 1.

For all linear regressions, the 95% confidence limits for the linear regression and the 95% confidence limits for the individual values were calculated. They were shown in each Figure. The equations used to calculate 95% confidence limits for individual \( Y \) are shown in Table 2.

**Discussion**

Many studies have been conducted to estimate the toxicity of chemicals using chemical or physical parameters. For example, the quantitative structure-activity relationship was studied in an attempt to estimate the toxicity of chemicals without performing toxicity testing. In other studies, many toxicity data were compared to search for a "law of toxicity" which may exist between chemicals. In a comparison of the hepatotoxicity of a large number of industrial chemicals, Lundberg et al. used the \( LC_{50} \) and \( LD_{50} \) values to determine the doses for hepatotoxicity testing. In the present study, we calculated the degree of correlation between \( LC_{50} \) and \( LD_{50} \) values to investigate the possibility that \( LC_{50} \) values could be estimated from \( LD_{50} \) values.

Chemical substances appear to exert their toxic effects in various ways depending on the means of exposure, such as inhalation, oral, or intraperitoneal administration. In inhalation exposure, chemicals enter the body through the lungs, whereas in oral or intraperitoneal administration, chemicals are adsorbed into the portal vein. Despite the different modes of chemical absorption involved, however, the \( LC_{50} \) values were well correlated with \( LD_{50} \) values for both oral and intraperitoneal administration in rats and mice. These results suggest that the exposure route has little effect on toxicity at high doses such as \( LC_{50} \) or \( LD_{50} \).

For both rats and mice, we obtained higher correlations between \( LC_{50} \) and i.p. \( LD_{50} \) than between \( LC_{50} \) and oral \( LD_{50} \). In inhalation exposure, transfer of inhaled chemicals from alveolar air into the blood is likely to be rapid, and in intraperitoneal injection, chemicals are adsorbed rapidly into intraperitoneal blood vessels. In oral dosing, the transfer of chemicals from the digestive tract into the blood is not as rapid. The \( LD_{50} \) values of chemicals are probably influenced by factors such as metabolic velocity and exhalation from the lungs when adsorption is relatively slow. Chemicals adsorbed through the digestive tract are readily metabolized in the liver. Moreover, a certain amount of the ingested chemicals may be excreted in feces. These are probably
Fig. 2. Correlation of LC₅₀ values in inhalation exposure and LD₅₀ values in intraperitoneal administration in rats
Units of ordinate and abscissa are as in Fig. 1.
Fig. 3. Correlation of LC₅₀ values in inhalation exposure and LD₅₀ values in oral administration in mice

Units of ordinate and abscissa are as in Fig. 1.
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Fig. 4. Correlation of LC₅₀ values in inhalation exposure and LD₅₀ values in intraperitoneal administration in mice. Units of ordinate and abscissa are as in Fig. 1.
the main reasons why correlations between LC50 and oral LD50 are lower than those between LC50 and i.p. LD50. A high correlation between LC50 and i.p. LD50 values suggests that i.p. LD50 values are more appropriate than oral LD50’s for estimating inhalation LC50 values from LD50 values.

The correlations were improved by using mmol/kg rather than mg/kg as the unit for LD50 values. This is probably because the toxicity depends on the number of molecules (mmol) that enter the body and not on the weight (mg) of the chemicals. Therefore, mmol appears to be more appropriate than mg as the unit of dose in toxicity experiments.

The correlations were also improved by using ppm h rather than ppm as the unit for LC50 values. This result was expected, because toxicity depends on both exposure concentration and exposure time. However, the correlations between LC50 and i.p. LD50 values in mice were not improved by converting the unit of LC50 from ppm to ppm h. This may be because the bodies of mice were too small to exhibit the chemical accumulation effect under inhalation conditions.

The correlation between LC50 and LD50 values was always higher in rats than in mice. There exist many differences in factors affecting the absorption efficiency of inhaled chemicals between rats and mice. As the animal increases in size, so do the nasal cavities, trachea, bronchi, and lungs. This may increase the efficiency of chemical absorption. It is necessary to consider the differences in structure, lobulation, and terminal airways, as well as in function, posture, chest wall compliance, and mechanical reflexes. Differences between rats and mice in dermal absorption, lung absorption coefficient, breathing frequency, and respiratory volume may affect lethal doses for inhalation exposure.

High correlations between LC50 and LD50 values in rats suggest that rats are more suitable than mice for extrapolating lethal doses of chemicals for inhalation exposure from those for oral or intraperitoneal administration.

The results obtained in our study indicate that it is possible to estimate an LC50 value for a chemical, accompanied by a range of confidence limits, from an LD50 value.

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References


4) Registry of Toxic Effects of Chemical Substances (RTECS) 1995, NIOSH, Cincinnati, Ohio.


