Application of Clearance Concepts to the Assessment of Exposure to Lead in Drinking Water

FREDERIC Y. BOIS, PHARMD, THOMAS N. TOZER, PHD, LAUREN ZEISE, PHD, AND LESLIE Z. BENET, PHD

Abstract: This paper explores the application of clearance concepts to environmental toxicology. Lead, for which a clearance of about 0.5 ml/min is estimated from published data, is chosen as an example. An index for the contribution of drinking water to total exposure is developed using these concepts. For lead, this index is shown to increase with the concentration of the metal in water; it is higher for children than for adults. At the maximum contaminant level (MCL) of 10 μg/L proposed by the US Environmental Protection Agency (EPA), the average contribution from lead in drinking water is estimated to be 7 percent. The contribution in children is about twice as great. At and above the current MCL of 50 μg/L, drinking water becomes a major source of lead exposure. (Am J Public Health 1989, 79:827–831.)

Introduction

Regulatory standards, developed to protect the public's health, usually take neither variability in exposure nor sensitivity of subpopulations explicitly into account. Furthermore, the contribution from a particular contamination source (e.g., drinking water) is typically not evaluated with respect to its impact on the overall human exposure. A simple approach based on clearance concepts can provide an index of interindividual sensitivity, as well as an indication of the contribution to exposure by a particular source. Although clearance concepts are familiar to most clinicians, they are utilized to a much lesser extent for regulating environmental contaminants. The purpose of this paper is to explore this potential application.

The example for our purpose is lead. The common sources of lead are: drinking water, by corrosion of lead pipes and lead solders; air from the combustion of leaded gasoline; and soils, from the degradation of lead paints.[1–3] The toxicity of lead in humans has been extensively studied.[4–14] Even at low levels, cardiovascular changes in children's learning and behavior abnormalities are among several effects that are of concern. To limit human exposure, the US Environmental Protection Agency (EPA) has set a drinking water standard of 50 μg/L.[15] The same standard has been recommended by the World Health Organization.[16] This limit and the new value proposed by the EPA for lead in drinking water (10 μg/L at the tap, 5 μg/L entering the distribution system)[15] are subsequently evaluated with respect to the contribution of this source of lead to overall exposure using clearance concepts.

Clearance Concepts

The extent of exposure to pollutants can be assessed in terms of the blood concentration. There are many determinants of this concentration, including both absorption and elimination. Clearance is the most useful of the elimination parameters. Knowing the blood concentration under steady-state conditions, the daily intake can be estimated or, conversely, the blood concentration can be predicted when the rate of intake is known. The former use of clearance is emphasized in this paper.

Clearance, CL, is the proportionality constant between the rate at which the body eliminates an environmental toxicant, and its blood concentration, Cb. Under steady-state conditions the rate of elimination is equal to the rate of intake, Rt. Clearance is then a parameter (assuming first-order elimination) that relates blood concentration to the rate of intake; that is,

$$\text{Rate of intake} = Rt = CL \cdot Cb \qquad (1)$$

Consider a constant concentration, Cw, of lead in the water supply. The rate of intake of lead from drinking water, Rw, is the product of three terms: F, its availability or fraction absorbed into the general circulation, Qw, the water volume intake per day, and Cw. At steady-state, when water is the only source of exposure to the contaminant,

$$\text{Rate of intake} = Rw = F \cdot Qw \cdot Cw = CL \cdot Cb$$

or

$$Cb = (F \cdot Qw \cdot Cw)/CL \qquad (2)$$

Thus, under steady-state (or chronic) conditions the lead blood concentration is a function of water intake, lead concentration in the water supply, and lead blood clearance. Clearance is a property of both the administered compound and the individual receiving the compound.

Clearance concepts can be used to assess the contribution of a given source to the total exposure to a substance. Another use is to determine interindividual variability in both the exposure of handling of a toxicant. A third application is to aid in the determination of hazardous levels of toxicants. The first of these applications follows.

Given an estimated clearance value for a compound (CL_{ref}), measurements of blood concentrations in a local population, and drinking water concentrations to which the population is exposed, one can determine the fraction of total intake that can be attributed to drinking water. This fraction, Iw, is an index of contribution of drinking water to the input from all sources ($CL_{ref} \cdot Cb$):

$$Iw = Rw/Rt = (F \cdot Qw \cdot Cw) / (CL_{ref} \cdot Cb) \qquad (3)$$

This ratio ranges theoretically from 0 to 1.

Address reprint requests to Thomas N. Tozer, PhD, Professor of Pharmacy and Pharmaceutical Chemistry, University of California-San Francisco, School of Pharmacy, San Francisco, CA 94143-0446. Dr. Bois and Benet are also with the School of Pharmacy at UCSF; Dr. Zeise is with the California Department of Health Services/RCHAS, Annex 2, Berkeley, CA 94704. This paper, submitted to the Journal, February 27, 1988, was revised and accepted for publication October 20, 1988.

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Methods

Determination of Total Blood Lead Clearance

For analysis of isotopic tracer lead experiments, in which total input was controlled, equation 2 was used. When exposure to lead was not strictly controlled, the relationship between lead concentrations in blood and drinking water were determined by least-square regression, using a modification of equation 2. In this case, the rate of total lead intake Rt is comprised of two terms: a known exposure term *Rw* (through drinking water) and another term *Rc* accounting for concomitant (e.g., airborne, occupational) exposures.

According to equation 1:

$$\text{Rate of intake} = Rw + Rc = F \cdot Qw \cdot Cw + Rc = CL \cdot Cb$$

or

$$Cb = (F \cdot Qw/CL) \cdot Cw + Rc/CL \qquad (4)$$

Rc can be considered to be independent of *Rw* and the slope of the regression line of *Cb* on *Cw* gives *CL/F*.

Determination of the Index of Contamination

Equation 3 was used for all these determinations. The water and blood concentrations were obtained from the reports cited. Literature values[17] of water volume intake per day—2 L for adults (over the age of 15), 1.4 L for children, and 0.9 L for infants (under the age of 2)—were used. Values of 20 percent for adults and 40 percent for children and infants were assumed for the fraction absorbed *F*. These values are based on studies of the absorption of small amounts, less than 500 μg/day, of lead given orally in the diet. Absorption was on the order of 10 percent for normal, non-fasting adults[18] while, on an empty stomach, absorption can be 35 percent.[19] For children and infants, oral absorption has been observed to be higher, 40 to 50 percent.[2,20,21] These values can vary considerably from one individual to another.[20]

The reference clearance for children and infants has been obtained by scaling the value for a 70-kg adult using the empirical relationship:

$$CL_{ref}(\text{child}) = CL_{ref}(\text{adult}) \cdot [(\text{Body weight in kg})/70]^{0.7} \qquad (5)$$

This relationship corrects for differences in renal function under the assumption that lead clearance varies directly with renal function.[22]

The relationship between lead concentration in water and the index of contamination has been assessed by least-square regression. The difference between children and adults was tested by analysis of variance with a 5 percent significance level.

Results

Blood lead clearance and the contribution of drinking water to the total exposure of various populations, for which sufficient data are reported, are as follows.

Reference Value for Blood Clearance: Experimental Determination

Two sets of controlled experiments allow for a determination of reference values for blood lead clearance (see Table 1).

The first set of value is based on experiments previously performed.[23–29] Three male subjects were administered fixed amounts of lead in water drunk with each meal, for one to three years. Steady-state concentrations were reached. Data included the administered dose (300, 1000, or 2000 μg Pb/day), estimates of lead contained in the diet (derived from diet samples), as well as measurements of blood lead concentrations before and after exposure. The regression of blood lead concentration on daily intake gives a clearance estimate (inverse of the slope) of 0.7 ml/min (0.14 S.E.) assuming that, on average, 20 percent of the lead ingested is absorbed (i.e., F = 0.2). This calculation takes into account lead contributions from other sources, which were not controlled during the experiment itself.

TABLE 1—Blood Clearances for Lead Determined from Experimental Data of the Literature

Clearance (ml/min)	Remarks	Reference
0.7 ± 0.14	Subjects SW, MR, and EB	23–29
0.392	Subject — A	18,30
0.570	— B	—
0.324	— D	—

In the second set of experiments in human subjects,[18,30] ^{204}Pb nitrate was added in the diet. Experiments on three subjects lasted 104, 124, and 83 days, respectively. Although these exposures were of shorter duration than for the subjects of the first set of experiments, blood lead concentration-time profiles showed that steady-state conditions were nearly attained. Rather than supplementing the diet with lead, a fraction of the normal dietary intake of 300 μg/day was replaced with ^{204}Pb. Under these conditions, clearances were 0.392, 0.570, and 0.324 ml/min, respectively, for the three subjects with a mean value of 0.429 (coefficient of variation: 17 percent).

Lead Clearance Estimated from Epidemiological Surveys

Alternatively, lead clearance may be estimated from epidemiological studies in which individual lead concentrations in blood and drinking water are surveyed. Table 2 presents values obtained for various data sets using linear regression.

A regression performed on the first set of data[31] indicates a clearance of 0.44 ml/min (0.008 Standard Error) for males and 0.38 ml/min (0.008 SE) for females in a French population (correlation coefficient: 0.97). Exposures corresponded to lead concentrations in drinking water ranging from 0 to 400 μg/L, with a geometric mean of 160 μg/L.

Lacey, *et al,* analyzed the relationship between water lead concentration and blood lead in three-month-old infants.[32] The slope they determined corresponds to a clearance of 0.36 ml/min (0.07 S.E.); the correlation coefficient

TABLE 2—Blood Clearances for Lead Determined from Regressions of Published Epidemiological Data

Clearance (ml/min)	Standard Error (%)	N	Remarks	Reference
0.44	2	121	Males	31
0.38	2	132	Females	—
0.36	22	104	Infants	32
0.44	10	881	Males	33
3.8	NA	109	Females	34
1.8	NA	75	First draw water	35
1.2	NA	75	Running water	—

(NA: not available)

was not reported. Water lead concentration ranged from 0 to 600 μg/L. Total water intake was approximately 0.8 L/day, including water taken in infant formula. It is important here to correct for water intake and increased lead absorption in children (F = 0.4).

Blood and water lead levels in 24 British towns have been reported.[33] Mean water concentrations for the different towns ranged from 0 to 350 μg/L. In this concentration range the clearance is 0.44 ml/min (0.045 SE) and the correlation coefficient is 0.98.

A clearance of 3.8 ml/min is indicated in another source.[34] The standard deviation cannot be estimated from the data presented; it should be large, as indicated by a low correlation coefficient (0.36). It is also not certain how the points were weighted in the regression. Both these limitations apply to a further source of data[35] for which clearance values of 1.8 and 1.2 ml/min are estimated when first flush or running water samples, respectively, were used for assessing exposure. Correlation coefficients here were 0.76 and 0.72, respectively.

With the exception of the data from the earliest studies,[34,35] there is general agreement between the regression data and the values observed in controlled experiments. A blood clearance for lead of 0.5 ml/min for a 70-kg adult, with a range of 0.3 to 0.8 ml/min, therefore, seems reasonable. This value is used in the next section for determining the importance of lead in drinking water to an individual's overall exposure.

Contribution of Drinking Water to Total Exposure

The literature on lead measured in both an individual's blood and drinking water has been surveyed.[31,35–50] This survey is available from one of the authors (Tozer) upon request. These data allow estimation of *Iw* values.

The calculated index values range from 0.005 (0.5 percent) to 6.4 (640 percent) (values higher than 1 at high exposure may result from overestimation of the fraction absorbed or an underestimation of clearance). Figure 1 shows the frequency distribution of Iw; for 50 percent of the population, drinking water contributes at least 15 percent to the total exposure to lead, at least in our sample data. Figure 2 presents the relationship between Iw and the corresponding lead water concentration (in μg/L). Because of the apparent log-normal distribution of Iw and water lead concentration, the regression was performed using natural logarithms. When several measures of water lead concentration (e.g., first flush or running samples) were provided for the same population group, the median value was selected. The correlation coefficient for the regression was 0.90.

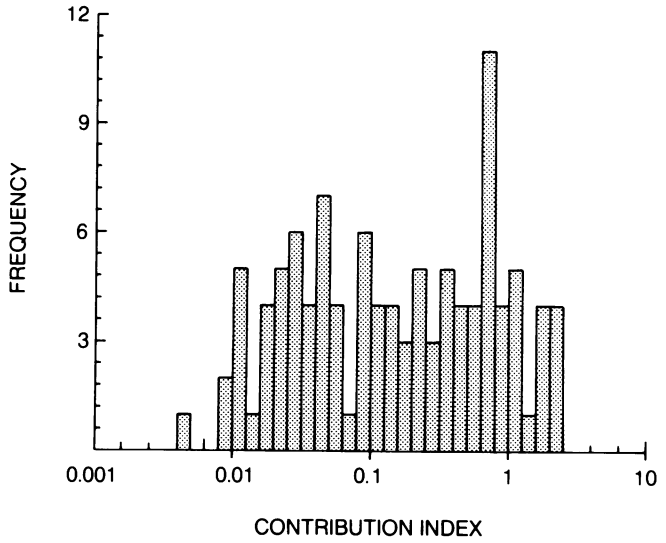

FIGURE 1—Distribution of the Index Iw of the Contribution of Lead in Drinking Water to Total Exposure, Determined from Epidemiological Data of the Literature (The Iw values are presented on a logarithmic scale).

Discussion

A clearance value obtained under steady-state conditions can be a useful indicator of the relative importance of chronic exposure to an environmental contaminant. Yet this concept has limitations and cannot be universally applied to all chemicals under all circumstances. As an example, consider compounds which are rapidly metabolized and/or excreted in the urine. A dynamic equilibrium is reached in which the blood concentration fluctuates dramatically over the day as a result of discontinuous intake (for drinking water) and high clearance. The proper assessment of a blood concentration would be difficult in this case. Lead, with its low clearance, does not fall into this category.

When a metabolite is primarily responsible for the toxicity, the use of the clearance of the parent compound as an indicator of individual sensitivity may be misleading. For example, a high clearance, for a given parent compound, could reflect a high rate of metabolite formation rather than a high renal excretion. This would imply an elevated target tissue dose, exactly contrary to what might be expected for the clearance value of the parent compound. Again, lead is not subject to this limitation.

Ideally the use of clearance concepts requires steady-state conditions and the presence of linear kinetics for distribution and disposition of the compound throughout the range of experimental and environmental exposures. For the majority of environmental contaminants, the assumption that levels of chronic exposure to a substance in air or water are

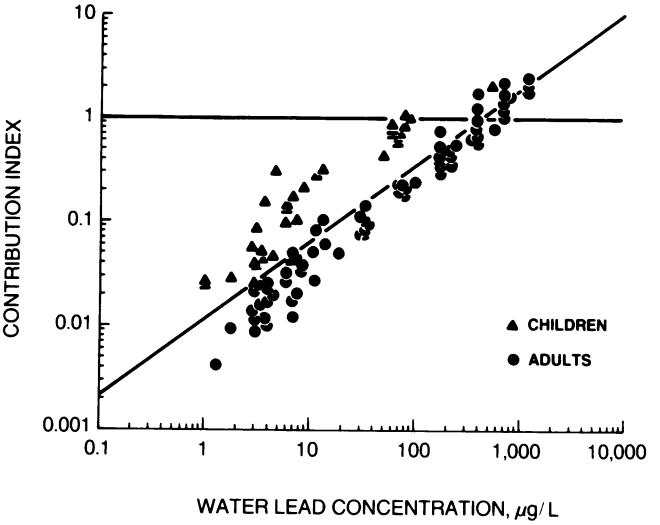

FIGURE 2—Regression of the logarithm of Iw on the logarithm of the lead concentration in water.
Data were obtained from published data in the literature. The regression equation is: ln (Iw) = −4.38+0.731·ln (lead concentration). The standard errors for slope and intercept are 0.0354 and 0.139, respectively. The correlation coefficient is 0.896.

below the values at which nonlinear behavior is observed is probably reasonable.

A nonlinear relationship seems to exist between blood lead and water lead concentrations at high exposures for humans.[33,36] Animal data indicate a possible saturation of blood lead levels.[52–54] Nevertheless, below approximately 500 μg/L the form of the relationship is nearly linear.[32] A clearance of 0.5 ml/min for adults is valid in this domain, and so are the results presented in Figures 1 and 2. Above 500 μg/L, Iw will be somewhat overestimated. A more mechanistic model[55–57] may more adequately describe the saturation of blood lead at high exposures. Two uptake mechanisms seem to be implied in intestinal lead absorption: a passive, non-saturable mechanism, and an active, saturable one.[5] A biphasic relationship between water lead and blood lead would be expected in this case. In this sense, the fact that the experimental clearance value determined in reference 23 (0.7 ml/min) is higher than that reported by Rabinowitz, *et al,*[18] could be explained by the much higher exposure in the former study.

Epidemiological studies may be used to estimate clearances through regression analysis. But high clearance values can be calculated if the intake of contaminated water is overestimated, for example by assuming a value of 2 L/day when the real value is much less. This situation may apply to the studies by Sherlock, *et al.*[49] A correct assessment of effective exposure is thus critical and a large population should be used.

Figure 2 shows that the contribution of lead in water to total lead exposure increases with its concentration at the tap. This relationship only occurs if the concentration of lead in drinking water correlates poorly with other sources of exposure and if drinking water is a major source of exposure. The lack of correlation of drinking water with other sources has also been reported.[50]

The spread about the regression line is quite large: the 95 percent confidence interval for estimates of Iw, at a given water concentration, span over a factor of 17. Therefore, for any particular water concentration the contribution of water to the total lead exposure cannot be calculated with accuracy. This variability may be explained by two factors. First, exposure is variable because water consumption is very different from user to user. We assumed standard values for different age groups.[17] Second, interindividual variability in lead absorption, distribution, and elimination clearly depends on individual factors.

It is not possible, in the absence of individual water consumption data, to separate these two sources of variation. To obtain a measure of interindividual variability, or identify different sensitive sub-groups, such information would be required. Nevertheless, in nearly all cases, the contribution of water to the overall exposure of lead is higher in children than in adults for the same water lead concentration. The fact that their intestinal absorption is higher by a factor of two contributes, together with their relatively higher water consumption, to this effect.

Note that for one-half of the population surveyed, waterborne lead represents less than 15 percent of the total exposure. The water for these populations contained only 30 μg/L or less of lead. When water lead concentration reaches 350 μg/L, on average 90 percent of total lead exposure arises from water. At the EPA MCL, 50 μg/L, about 20 percent of lead exposure in these populations is accounted for by lead in drinking water. However, at least 72 percent of lead exposure for 5 percent of the population might come from water contaminated with 50 μg/L of lead. This assumes a log-normal distribution (SE = 0.73) of *Iw* around the regression line.

We did not assume a dependence of lead clearance on urine flow. Under this hypothesis, the ratio Qw/CLref (in equation 3) would tend to have the same constant value for both adults and children. Such a flow dependence occurs when substances are extensively reabsorbed in the kidney tubules. Although lead seems to be partially reabsorbed,[58–61] renal clearance is not the only mechanism for lead elimination and the published data on renal lead handling in humans[62] suggest that lead clearance is not highly dependent on urine flow. To determine the impact of this flow hypothesis, we analyzed the effect of flow dependence. The difference between adults and children was reduced but still statistically significant.

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ADDENDUM

Detailed lists of water lead concentrations and contribution index, Iw, of water to total exposure as determined from published epidemilogical data are available upon request to the authors.

Baby Doe Decision-Making in the 1990s: Conference Announced

A national conference entitled "Baby Doe Decision-Making in the 1990s" has been scheduled for September 14–15, 1989 at the Center for the Study of Bioethics, Medical College of Wisconsin, Milwaukee. Topics will include the effects of cost constraint measures, fetal therapy, genetic screening, and AIDS on Baby Doe decision-making.

The conference—co-sponsored by the Wisconsin Ethics Committee Network, the Medical Ethics Resource Network of Michigan, the Minnesota Network for Institutional Ethics Committees, and the Iowa Hospital Association—will be held at the Sheraton Mayfair Hotel in Milwaukee, WI.

For further information, contact: Anne Marie Talsky, Center for the Study of Bioethics, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226. Tel: 414/257-8498.