

TRANSFER OF ^{131}I INTO HUMAN BREAST MILK AND TRANSFER COEFFICIENTS FOR RADIOLOGICAL DOSE ASSESSMENTS

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Abstract—Data on transfer of radioiodine into human milk are rare in the literature. Data from sixteen publications were reviewed and analyzed to estimate the transfer coefficient (f_{hm}^* , having units of d L^{-1}). The data on the radioiodine concentration in breast milk were analyzed by two methods: direct numerical integration and integration of a fitted exponential model. In general, the integrated fitted functions were greater. The fitted functions likely better describe the transfer into milk since few data sets sampled mothers' milk near the time of maximum excretion. The derived transfer coefficient values seem to represent two populations. The first group was those individuals who had very low excretions, including those where thyroid and mammary uptake was impaired by the administration of stable iodine or iodinated compounds. The second group included those with much higher excretions. The second group, termed the "normal-excretion" group, had transfers of iodine to milk that were more than ten-fold higher than in the "low-excretion" group. The derived milk transfer coefficient data for the low- and normal-excretion groups fitted to lognormal distributions gave geometric means, (geometric standard deviations), of 0.043 d L^{-1} (2.1, $n = 14$) and 0.37 d L^{-1} (1.5, $n = 12$), respectively. Estimates of the effective half-time (time from maximum concentration to half the value) were determined for the low- and normal-excretion groups separately. There was evidence that the effective half-time was longer for the normal- than for the low-excretion group; the geometric mean (and geometric standard deviation) were 12 (1.7) and 8.5 (2.6) h, respectively, though the difference was not statistically significant. The geometric mean times to maximum milk concentration in the low- and normal-excretion groups were nearly identical, 9.4 (3.1) and 9.0 (1.6) h, respectively. The data show that administration of large doses of stable iodine (commonly used to block uptake of iodine into the thyroid) is also an effective means to block radioiodine transfer into milk. Thus, protecting the mother's thyroid also protects the nursing infant. Despite inadequacies of available data

describing the transfer of radioiodine to human milk within a healthy population of women, the values of f_{hm}^* provided here are believed to be the best available for use in radiological assessments. These values are particularly applicable to lactating women having normal diets and availability to stable iodine, as in the United States.

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Key words: milk; ^{131}I ; transfer coefficient; dose assessment

INTRODUCTION

A QUANTITATIVE evaluation of the transfer of radioiodine into human milk has importance for conducting realistic radiological dose and risk assessments for nursing infants. This particularly applies when radioactive iodine has been released to the environment, such as from nuclear reactors or nuclear weapons tests. In many previously conducted radiological assessments, the dose to an infant's thyroid from consumption of radioiodine-contaminated human milk has either been ignored or relied on very limited literature data to derive parameter values for estimating the transfer to the nursing child. This paper examines published data on the transfer of radioiodine into human milk, estimates milk transfer coefficient values, and discusses their application to estimating the transfer of radioiodine to the nursing infant. This paper recommends values for use in future assessments where the transfer of ^{131}I into human milk is of concern.

Iodine is an indispensable part of thyroid hormone, which is required for metabolism, growth, and development of all mammals and is normally furnished to humans during infancy via maternal milk. Hence, accurately assessing radioiodine in human milk is important because environmentally transferred iodine is biologically concentrated into the milk and will be further concentrated into the thyroid gland of a nursing infant. The thyroid glands of infants, of course, are small and relatively radiosensitive compared to those of adults (Ron et al. 1995).

Iodine intake in adults is normally through ingestion of food products, with the highest concentrations generally found in seafood, cows' milk, some plant products, and iodized salt. There is significant regional variability

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of the iodine content of soil, resulting in variability of plant concentrations and, hence, dietary availability. Small amounts of iodine are available in drinking water and through inhalation, particularly in windy coastal areas (Mellor 1956).

If radioiodine from nuclear fission is released into the environment, it is mixed indiscriminately with naturally stable iodine of the diet, air, and water. Under such conditions, human and animal milk continually select and concentrate iodine, both stable and radioactive. All animals ingesting that fresh milk will receive the concentrated iodine isotopes.

The normal human body contains about 9 to 10 mg of iodine with about 85–90% in the thyroid gland (Riggs 1952). The thyroid concentrates more than 100 times the daily requirement, secreting into the blood about 1% each day as hormone. The iodide ion is selectively concentrated from body fluids into the thyroid and other specific cells (Carrasco 1993) by a powerful biological selector, the sodium-iodide transporter, also called a "symporter" (abbreviated as NIS; see Dai et al. 1996; Smanik et al. 1996; Spitzweg et al. 2000; Tazebay et al. 2000). The symporter is sodium dependent and was first cloned in the mid 1990's from thyroid tissue of rats (Dai et al. 1996) and from human beings (Smanik et al. 1996).

At the termination of pregnancy, a similar iodide transporter in the mammary gland (abbreviated mgNIS; see Tazebay et al. 2000) is stimulated, lactation begins, and iodide is concentrated in the milk produced by the mother. At the same time, the thyroid of the newborn infant is stimulated to retain 46–97% of the iodine ingested (VanMiddlesworth 1954).

The capacity of the mammalian breast to actively accumulate iodide is a function shared with the thyroid gland as well as certain other tissues, including the salivary gland, gastric mucosa, skin, and placenta (Spitzweg et al. 2000). The transporters in thyroid and mammary glands are similar but separate pituitary hormones control their operation independently. Both glands use the electrochemical gradient across the cell membrane to transport two different ions—sodium and iodine—in the same direction (Welsh and Mankoff 2000). Spitzweg et al. (2000) provide details of the biochemistry of thyroid iodine transport.

The normal concentration of stable iodine in human milk was reported by the ICRP (1975) to be $20 \mu\text{g L}^{-1}$ to $150 \mu\text{g L}^{-1}$ with a mean of $70 \mu\text{g L}^{-1}$. Similar values were reported by the Institute of Medicine (IOM 1991), $110 \pm 40 \mu\text{g L}^{-1}$, though the mean concentration at some locations in the United States during the 1980's was higher, about $180 \mu\text{g L}^{-1}$. Concentrations of iodine in human milk up to $700 \mu\text{g L}^{-1}$ have occasionally been reported (Gushurst et al. 1984). Measurements of iodine concentration of breast milk in Spain in the early 1990's indicated a mean of $100 \mu\text{g L}^{-1}$. Those data indicated that there was no difference in concentrations among mothers who delivered infants prematurely compared to those who delivered full-term (Ares et al. 1994).

The daily dietary requirement of iodide in lactating women is about 30% higher than for the general public ($200 \mu\text{g d}^{-1}$ vs. $150 \mu\text{g d}^{-1}$) (IOM 1991) primarily to satisfy the requirement for milk production (Gorman 1999; NRC 1989). Iodine can of course be provided to the nursing child via infant formula. However, data published by Ares et al. (1994) indicate that most commercial formulae do not provide adequate amounts of iodine and many are far below the recommended levels. Smyth (1999) has also recognized that problem.

Various biologic and metabolic parameters have been considered as possibly important to the excretion of radioiodine via breast milk, one being the milk production rate. However, the daily volume of milk produced by lactating women and ingested by infants averages over a narrow range, from about 750 to 800 mL d^{-1} (IOM 1991). This volume varies little among women with different caloric intakes, nutritional status, age, parity, and anthropometric indices though the volume of milk secreted declines rapidly if suckling is discontinued. Thus, it may be that milk production rate within *homo sapiens* is not a significant determinant of iodine transfer to milk.

Since the early-1950's when ^{131}I became available for research purposes, investigations have been conducted to quantify the partitioning of iodine in tissues and secretions of animals and humans (Honour et al. 1952; Brown-Grant 1961). During the years of atmospheric nuclear weapons testing, the concern over public exposure to radioactive isotopes (primarily cesium, strontium and iodine) in cows' milk led to the concept of the milk transfer coefficient. The origin of the transfer coefficient can be traced to Ward et al. (1965) and Johnson et al. (1968) where the transfer of radioactive cesium into cows' milk was investigated (also see Ward and Johnson 1986, 1989). They defined the transfer coefficient to be the quotient of the equilibrium concentration of the radionuclide in milk and the intake rate assuming constant daily intake. Later, for the purposes of developing radiological assessment models, a symbol was assigned to the milk transfer coefficient for dairy cows, f_m (or sometimes f_m^* to delineate the transfer of a radioactive rather than stable isotope) by Ng et al. (1982). In this work, we use f_{hm}^* to denote the transfer coefficient that describes excretion into human milk.

The transfer coefficient has been extensively reported for bovine and goat milk, but only three previous studies were found that estimated the transfer coefficient for lactating women. In a study of the relationship between thyroid dose from NTS fallout and thyroid disease prevalence among Utah residents (UU 1992; Simon et al. 1990), a median f_{hm}^* value of 0.02 d L^{-1} was estimated based on data from three publications. Later, based on data in a single publication, the Hanford Dose Reconstruction Project derived a uniform probability distribution to describe the mothers' milk transfer coefficient with a minimum of 0.07 and maximum of 0.36 d L^{-1} (Snyder et al. 1994). Finally, the National Cancer Institute in a study of thyroid doses received from NTS

fallout by representative persons in all counties of the U.S. (NCI 1997), derived a lognormal uncertainty distribution for f_{hm}^* (called f_{mm}^* in that work) with a geometric mean value of 0.12 d L^{-1} and geometric standard deviation of 2.9. That assessment was based on data in five publications, which included those used in the two previous studies. Data from 16 publications were reviewed for this work. The remainder of this paper discusses methods to interpret the literature data into estimates of the transfer coefficient, summarizes the data, and reports estimates of the transfer coefficient.

METHODS

Few literature data are available from which a quantitative determination of the transfer of radioiodine into the breast milk of healthy women can be determined. Much of the data are based on observations of women requiring medical care for conditions encountered postpartum; only a few were in the early stages of lactation. Those conditions included thyroid conditions, such as thyroiditis, Graves' disease (hyperthyroidism), hypothyroidism, carcinoma, as well as other abnormalities including hypertension, deep-leg thrombosis, and pulmonary embolism. Some of the data were not applicable to normal circumstances because women were given large dosages of stable iodine to block thyroid uptake of radioactive iodine or given large doses of iodinated compounds to visualize organ function. Others received large doses of radioiodine to ablate the thyroid. All of these treatments likely affect the normal transfer of iodine to milk.

Models of intake and excretion

In general, the time-dependent concentration in a well-mixed compartment can be found from a convolution of the intake rate of the radionuclide (Bq d^{-1}) and the retention function. Numerous authors have discussed that method which assumes a linear system; see for example, Peterson (1983) and Skrable et al. (1994). Because breast milk is not retained in the body, but normally leaves the body relatively quickly after it is produced, any iodine transferred to milk is by definition excreted. Hence, the retention of iodine in milk can be considered equivalent to its excretion via milk. From this point of view, the excretion function for radioiodine is denoted by $L(t)$ and is equal to the time-dependent *fraction of the input dosage excreted via milk*. Under the assumption that the milk production by the lactating woman is constant from day to day, the excretion function can be expressed in units of concentration (i.e., Bq L^{-1} per Bq intake) as is frequently done in pharmacological studies. The importance of determining $L(t)$ is because of its relationship to f_m^* , as defined under equilibrium conditions.

The convolution of the excretion function is related

to the radioiodine concentration in human milk, $C_{hm}(t)$, by

$$C_{hm}(t) = \int_0^t \dot{I}(\tau) L(t - \tau) d\tau. \quad (1)$$

Using eqn (1), we consider two simple cases: (1) the intake rate, $\dot{I}(t)$, is constant over time; and (2) the intake, I_0 , is a single spike, characterized by a near instantaneous input. In either case, it is possible to determine $L(t)$ in terms of measurable quantities, namely $C_{hm}(t)$ and \dot{I} .

Case 1. The intake rate, \dot{I} , is a constant and has units of Bq d^{-1} . Hence,

$$C_{hm}(t) = \dot{I} \int_0^t L(t - \tau) d\tau = \dot{I} \int_0^t L(\tau) d\tau. \quad (2)$$

For large t , the radioiodine milk concentration equilibrates; the concentration is denoted as \bar{C} with units of Bq L^{-1} . Hence,

$$C_{hm}(t) = \bar{C} = \dot{I} \int_0^t L(\tau) d\tau, \text{ for large } t. \quad (3)$$

And therefore:

$$\lim_{t \rightarrow \infty} \int_0^t L(\tau) d\tau = \frac{\bar{C}}{\dot{I}} = f_{hm}^*. \quad (4)$$

Eqn (4) shows that the milk transfer coefficient, f_{hm}^* , under the original definition, is equal to the integral of $L(t)$ for large t .

Case 2. The intake rate is characterized by a spike input over the interval $[0, \varepsilon]$, for $\varepsilon > 0$ (but very small). Thus, $\dot{I}(\tau)$ can be viewed as follows:

$$\dot{I}(\tau) = \begin{cases} \frac{I_0}{\varepsilon} & \text{on } [0, \varepsilon] \\ 0 & \text{at other times} \end{cases} \quad (5)$$

where I_0 is the total intake in units of Bq , and ε is the infinitesimal time for the spike input to be administered.

Using eqn (1) and the definition of the integral as the limit of a Riemann sum,[‡] we have

$$C_{hm}(t) = I_0 L(t). \quad (6)$$

Therefore,

$$L(t) = \frac{C_{hm}(t)}{I_0}. \quad (7)$$

[‡] More formally, $C_{hm}(t) = \int_0^t \dot{I}(\tau) L(t - \tau) d\tau$ can be written as the limit of a Riemann sum, $\lim_{n \rightarrow \infty} \sum_{i=1}^n \dot{I}(\tau_i) L(t - \tau_i) \Delta\tau$, where $\Delta\tau = \tau_i - \tau_{i-1} = (t - 0)/n$, over a partition of $[0, t]$. Now, letting $\Delta\tau$ get small, note that all terms in the summation vanish, except for those terms on $[0, \varepsilon]$; this sum is $I_0/\varepsilon L(t - \varepsilon)\varepsilon \cong I_0 L(t)$, since ε can be made arbitrarily small.

Since by eqn (4), f_{hm}^* was shown to be equal to the integral of $L(t)$, eqn (7) can be used to determine (or define) f_{hm}^* in the spike input case by integrating both sides with respect to time:

$$\int_0^t L(\tau) d\tau = \int_0^t \frac{C_{hm}(\tau) d\tau}{I_0} = f_{hm}^*. \quad (8)$$

It follows from eqns (4) and (8) that

$$\int_0^{t \rightarrow \infty} L(\tau) d\tau = \frac{\bar{C}_{hm}}{I} = \int_0^t \frac{C_{hm}(\tau) d\tau}{I_0} = f_{hm}^*. \quad (9)$$

By these arguments, there is a more general equivalent expression for the milk transfer coefficient and this allows deriving a numerical value from data acquired under steady-state conditions or from a single spike input. Lassey (1980) reached these same conclusions. The conclusion is important because most experimental data are available for the conditions of Case 2 (a spike input). However, there is sometimes a need in radiological assessments for a transfer coefficient for conditions of near constant intake (Case 1), e.g., for long-lived radionuclides.

By the above analysis, the milk transfer coefficient can be calculated in any of three equivalent ways, depending on the data available:

$$f_{hm}^* = \begin{cases} \frac{\bar{C}_{hm}}{I} & \text{(for a constant intake rate)} \\ \int_0^\infty \frac{C_{hm}(\tau) d\tau}{I_0} & \text{(for a spike input)} \\ \int_0^\infty L(\tau) d\tau & \text{(as the general form for either case)} \end{cases} \quad (10)$$

Therefore, the milk transfer coefficient is the proportionality constant between a constant intake rate, \dot{I} (having units of Bq d^{-1}), and the resulting equilibrium milk concentration \bar{C} (having units of Bq L^{-1}),

$$\bar{C}_{hm} = \dot{I} f_{hm}^*, \quad (11)$$

or the proportionality constant between a single intake, I (having units of Bq), and the time-integral of the activity excreted in milk (expressed on a concentration basis, having units of Bq d L^{-1}),

$$\int_0^\infty C_{hm}(\tau) d\tau = I_0 f_{hm}^*. \quad (12)$$

In both cases, the milk transfer coefficient has units of d L^{-1} .

For most radionuclides excreted from the body, the

excretion function, $L(t)$, generally decreases exponentially with time and often can be modeled as a summation of two or more exponential terms, so that

$$L(t) = \sum_{i=1}^n k_i e^{-(\lambda_d + r_i)t}.$$

In the excretion function shown here, λ_d is the radioactive decay constant [= $\ln(2) T_{1/2}^{-1}$] and r_i is the biological removal constant for the stable element from compartment i , where both constants have units of d^{-1} . Using this model of $L(t)$, f_{hm}^* can be calculated as

$$\begin{aligned} f_{hm}^* &= \int_0^t L(\tau) d\tau \\ &= \int_{t=0}^\infty \sum_{i=1}^n k_i e^{-(\lambda_d + r_i)t} dt \\ &= \int_{t=0}^\infty \sum_{i=1}^n k_i e^{-\alpha_i t} dt \\ &= \sum_{i=1}^n \frac{k_i}{\alpha_i} \end{aligned} \quad (13)$$

where $\alpha_i = \lambda_d + r_i$.

The data in the literature reviewed for this analysis varied in terms of its reported units: either as radioiodine concentration in mother's milk (Bq L^{-1}) at times after intake, or as values of the excretion function $L(t)$ (L^{-1}). In all cases, however, only excretion following a single intake was reported.

In this work, the milk concentration data were fit to a two-term exponential model:

$$C_{hm}(t) = (a_1 e^{-\alpha_1 t} - a_2 e^{-\alpha_2 t}) \quad (14)$$

where $C_{hm}(t)$ and a_1 and a_2 have units of Bq L^{-1} and represent concentrations in milk. Normalizing $C_{hm}(t)$ to the radioiodine dosage (I in units of Bq) gives $L(t)$:

$$\begin{aligned} L(t) &= \frac{C_{hm}(t)}{I} = \frac{(a_1 e^{-\alpha_1 t} - a_2 e^{-\alpha_2 t})}{I} \\ &= (k_1 e^{-\alpha_1 t} - k_2 e^{-\alpha_2 t}). \end{aligned} \quad (15)$$

Following the method of eqn (13) to determine f_{hm}^* , the time-integral of eqn (15) gives

$$f_{hm}^* = \int_{t=0}^\infty (k_1 e^{-\alpha_1 t} - k_2 e^{-\alpha_2 t}) dt = \left[\frac{k_1}{\alpha_1} - \frac{k_2}{\alpha_2} \right]. \quad (16)$$

The time to reach peak concentration following intake was predicted by taking the derivative of $C_{hm}(t)$, setting equal to zero, and solving for t . This time is denoted as

t_{max} . When the concentration as a function of time is modeled by eqn (14), the time to maximum concentration, t_{max} , is

$$t_{max} = \frac{\ln(a_2\alpha_2/a_1\alpha_1)}{(\alpha_2 - \alpha_1)}. \quad (17)$$

When the intake data reported in the literature was for an isotope of iodine other than ^{131}I , the estimate of f_{hm}^* was corrected to the half-life of ^{131}I by decay correcting each data point before the curve fitting step. The correction was done by multiplying each data point by the ratio of $\exp(-\lambda_{131}\Delta t)/\exp(-\lambda_{123}\Delta t)$ or $\exp(-\lambda_{131}\Delta t)/\exp(-\lambda_{125}\Delta t)$, depending on whether ^{123}I ($T_{1/2} = 13.3$ h) or ^{125}I ($T_{1/2} = 59.4$ d) was administered.

Analysis of data on radioiodine excretion via human breast milk. Data from sixteen published reports were analyzed though some papers described the excretion by more than one subject. The data represented 24 individuals plus seven subjects described by a mean value and another 26 subjects, also described by a mean value. Table 1 provides an overall summary of the literature data used for our analysis.

Much of the data were incomplete in that the entire time-dependence of excretion was not documented. In particular, investigators often missed sampling milk near the time of the peak concentration. Hence, two types of analyses were conducted here. First, reported time-dependent concentration data were numerically integrated using the trapezoid rule applied to linear functions between data points to approximate the integral value needed for eqn (13). In general, it was necessary to assign a concentration of zero at time zero because that datum was omitted in the published data. Second, the two-component exponential model (eqn 14) was fitted to the reported concentration data using software that implements an iterative regression technique, and the fitted function was integrated by the analytical solution shown in eqn (16).

The mathematical form of the equation to which the time-dependent concentrations were fit may imply certain characteristics about the underlying kinetics of iodine in the body; however, no specific pharmacokinetic model is assumed here. Eqn (14) fit most of the data sets well (typical R^2 values were >0.95), though for some data sets more complex equations might have been used. The two-term exponential model was most relevant for iodine administered intravenously. A three-component model would likely be more applicable to an oral administration, though the choice of model form would not have significantly changed the integral value of activity calculated and reported here.

RESULTS AND DISCUSSION

Data from the publications reviewed (see Table 1) were fit to model eqns (14) or (15). Because $C_m(t)$ must

be zero at $t = 0$, it follows that a_1 must equal a_2 . Hence, the model of eqn (14) can be reduced to

$$\begin{aligned} C_{hm}(t) &= a_1e^{-\alpha_1t} - a_2e^{-\alpha_2t} \\ &= a_0(e^{-\alpha_1t} - e^{-\alpha_2t}) \\ &= a_0(1 - e^{-(\alpha_2 - \alpha_1)t})e^{-\alpha_1t} \\ &= a_0(1 - e^{-\beta t})e^{-\alpha_1t}. \end{aligned} \quad (18)$$

The model form of eqn (18) is identical to that used by Vandecasteele et al. (2000) who studied the transfer of ^{131}I cows' milk following single injections of radioiodine. This model, as noted by Vandecasteele, has an attractive simplicity of interpretation in that β represents the absorption rate and α_1 represents the excretion rate. A three-term exponential model analogous to eqn (18) was used for fitting data from three publications for which there was too few data points to fit to eqn (14) adequately.

The f_{hm}^* values calculated using eqn (16), i.e., the integral of the fitted functions, are presented here as the preferred estimates. The mean (or median) of the 26 f_{hm}^* values in Table 1 calculated from fitting eqn (14) (see column labeled "Integral of fitted function") were larger by about 40% (12% for median) than values calculated directly by numerical integration (Table 1, column labeled "Integral of data"). The fitted equations should be more representative of the true excretion functions since some of the data sets did not contain measurements at all times. Fig. 1 is an example which demonstrates why the value of the integrated fitted function is sometimes larger than numerical integration by the trapezoid rule.

The empirical cumulative probability distribution for all 26 of the estimated f_{hm}^* values suggests two distinct populations: a very low-excretion group, and a group with significantly higher excretion (Fig. 2), termed the normal-excretion group. The data allowed 14 estimates of f_{hm}^* for the low-excretion group and 12 estimates to characterize the normal-excretion group.

Because of the noted differences in the transfer coefficient between the two groups, further analyses were done on each group separately. Table 2 provides summary statistics of the f_{hm}^* estimates. Four estimates of central tendency are given for each group: the mean, the median, the geometric mean, and a weighted average. The weighted average was calculated using the normalized reciprocals of the variance of each case as a weighting factor. For each subject, the variance was estimated from a propagation of errors of the coefficients fitted to eqn (14).

The low-excretion group included three f_{hm}^* values for individuals who first received large doses of stable iodine to block thyroid uptake of the administered radionuclide. Of those three f_{hm}^* estimates, two were based on excretion data from single subjects; the third was based on the mean excretion for a group of seven lactating women. The group given stable iodine to block thyroid uptake exhibited low excretion of the radionuclide into milk—in agreement with recent literature that

Table 1. Summary of references and derived parameters, ordered by the magnitude of the *Integral of the Fitted Function*. All derived data values are decay corrected to ¹³¹I. Horizontal line separates low-excretion and normal-excretion groups.

Authors	Year of publication	Nuclide	Activity administered (MBq)	Mode of administration	Nuclide labeling	Subject	Time post-partum	Circumstances	Integral of data	Integral of fitted function	<i>t</i> _{max} (h)	Effective half-time (h)
Kettle et al.	1994	¹²³ I	160	intravenous	meta-iodobenzylguanidine (MIBG)	—	12 wk	patient investigated for possible phaeochromocytoma, thyroid blocked with Lugol's iodine renography	0.0073	0.0078	9.4	6.8
Rose et al.	1990	¹²³ I	9	?	hippuran	#2	7 mo	renal dysfunction	0.053	0.012	4.2	3.1
Ahlgren et al.	1985	¹³¹ I	0.3	intravenous	hippuran	#2	?	hypertensive patient with possible renal dysfunction	0.017	0.025	7.7	6.1
Mounford and Coakley	1989a	¹³¹ I	22	intravenous	OIH	—	8 wk	suspected pulmonary embolism	0.032	0.032	2.2	1.8
Wyburn	1973	¹³¹ I	7.4	intravenous	MAA	#2	3 mo	suspected postpartum thyroiditis	0.044	0.048	19	13
Hedrick et al.	1986	¹²³ I	6.8	?	hippuran	—	7 wk	—	0.041	0.049	5.5	4.7
Karjalainen et al.	1971	¹³¹ I	0.93	intravenous	ortho-iodohippuric acid (OIH)	#2 (avg. value for 25 mothers)	2-5 d	—	0.027	0.053	8.0	6.3
Mattson et al.	1981	¹²³ I	4.1	intravenous	fibrinogen	—	4 d	suspected deep venous thrombosis, thyroid blocking dosage of pertechinate administered	0.035	0.054	52	45
Ahlgren et al.	1985	¹³¹ I	0.3	intravenous	hippuran	#1	?	renal dysfunction	0.060	0.055	2.5	4.2
Rose et al.	1990	¹²³ I	10	?	hippuran	#1	18 d	renography	0.011	0.064	1.9	5.3
Karjalainen et al.	1971	¹³¹ I	11	intravenous	Macro-aggregated human serum albumin (MAA)	#1 (avg. value for 7 mothers)	?	thyroid blocked with KI	0.060	0.072	18	13
Bland et al.	1969	¹²³ I	0.37 in 2 doses	intravenous	Serum albumin	#1	few days	caesarean section delivery	0.075	0.10	43	31
Palmer	1979	¹²⁵ I	3.7	intravenous	fibrinogen	—	following caesarian section	suspected deep leg-vein thrombosis, thyroid blocked after dosage	0.12	0.12	43	32
Weaver et al.	1960	¹³¹ I	0.37	oral	probably carrier-free	#2	close to weaning	—	0.11	0.15	13	12
Miller and Weetch	1955	¹³¹ I	1.1	oral	probably carrier-free	—	4 mo	suspected thyrotoxicosis	0.20	0.25	6.4	10
Spencer et al.	1986	¹³¹ I	190	oral	sodium-iodide	—	6 mo	diagnostic whole-body scanning, hypothyroid patient data taken after therapeutic dose and a previous thyroidectomy (patient with papillary cancer)	0.25	0.25	8.6	9.5
Rubow and Klopper	1988	¹³¹ I	5,100	?	?	—	8 mo	—	0.25	0.28	8.8	7.6
Numberger and Lipscomb	1952	¹³¹ I	3.7	oral	carrier-free	#2 (only)	4 mo	—	0.29	0.28	5.3	7.0
Wyburn	1973	¹³¹ I	7.4	intravenous	MAA	#1	3 d	pulmonary embolism 3 d after caesarean section	0.27	0.28	23	18
Dydek and Blue	1988	¹³¹ I	0.32	oral	sodium-iodide	#1	4 mo	30-y-old woman with Graves' disease (hyperthyroid), first data taken after diagnostic dose	0.31	0.32	6.3	5.1
Robinson et al.	1994	¹³¹ I	200, followed by 4,000	?	?	—	2 week +	clinically hypothyroid before diagnosis, concentrations measured after near-total radiation ablation for follicular thyroid cancer	0.27	0.41	7.1	12
Dydek and Blue	1988	¹³¹ I	0.36	oral	sodium-iodide	same subject, 2nd dosage	5 mo	30-y-old woman with Graves' disease, second data taken after therapeutic dose	0.49	0.41	7.9	13
Weaver et al.	1960	¹³¹ I	0.37	oral	none	#3	close to weaning	—	0.39	0.46	9.1	13
Weaver et al.	1960	¹³¹ I	0.37	oral	none	#6	close to weaning	—	0.20	0.48	18	28
Weaver et al.	1960	¹³¹ I	1.1	oral	probably carrier-free	#1	close to weaning	—	0.49	0.48	4.8	8.4
Bland et al.	1969	¹²⁵ I	0.22	intravenous	Serum albumin	#2	few days	surgically sterilized at time of delivery	0.33	0.89	19	32

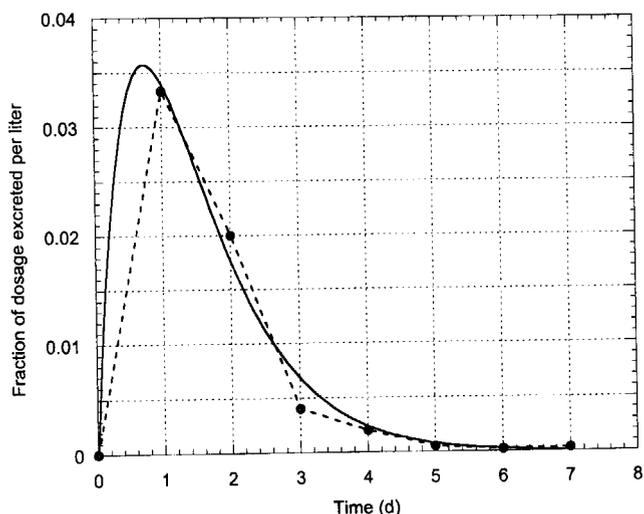


Fig. 1. Comparison of milk excretion data (Karjalainen et al. 1971, connected by dashed line) and fitted two-term exponential function (solid line).

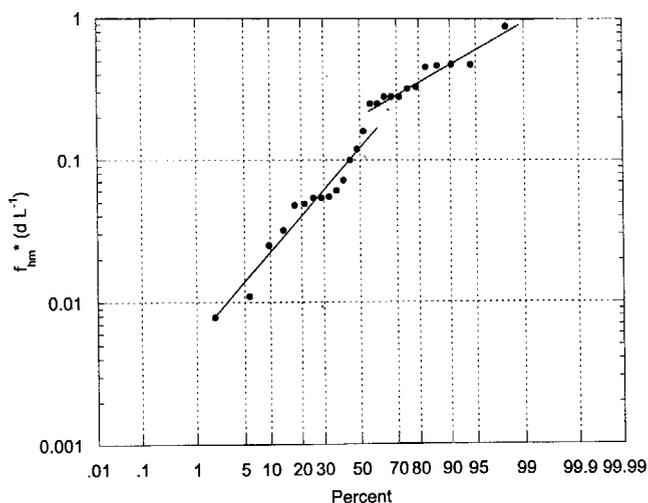


Fig. 2. Empirical cumulative distribution of f_{hm}^* values for ^{131}I transfer into human milk showing possible division into two populations.

indicates that blocking uptake into the thyroid gland by administration of stable iodine also results in blocking iodine uptake into the milk of the mammalian breast (Dai et al. 1996). In some of the cases, large doses of iodinated compounds were administered; these compounds slowly became deiodinated and continually overwhelmed (not necessarily blocked) the mammary gland symporter.

The remaining eleven estimates of f_{hm}^* in the low-excretion group were based on data for ten individuals and a mean value for 25 others. None of those 35 individuals received blocking doses of stable iodine. Finding a single condition to explain the low excretion for these latter subjects is difficult. A common medical condition affecting this group was renal dysfunction.

However, there is no obvious association between renal dysfunction and low transfer of iodine to milk. It is more likely that the chemical form of the administered radioiodine explains the low iodine transfer.

A number of chemical forms of radioactive iodinated compounds were administered to the subjects whose data were reviewed in this paper (Table 1). The forms of iodine that were of the simplest chemical nature (e.g., carrier-free and sodium-iodide) were found only in the normal-transfer group. Other forms of iodine including meta-iodobenzylguanadine (MIBG), hippuran, ortho-iodohippuric acid (OIH), and fibrinogen were found exclusively in the low-transfer group. This suggests the chemical form of the administered radioactive iodine plays a role in the total amount and possibly the quantity of the radionuclide that is excreted via breast milk. Presumably, a longer time is required for the breakdown of some forms. Arguably, iodine in the complex chemical forms will be eliminated more effectively by urinary and fecal excretion, thus leading to a reduced transfer of iodide to breast milk via the symporter. Radioiodine that is ingested from environmental releases, generally of ionic or simple organic forms (such as methyl iodide), would result in excretion similar to the normal-transfer group.

It should be noted here that in a strict sense, saturation of the mgNIS by large intakes of stable iodine, leading to blocking or impairment of the symporter, results in a form of non-linear kinetic behavior. Such circumstances would invalidate the underlying linear system assumptions that lead to eqn (14). In such cases, predicted values of $C_{hm}(t)$ from f_{hm}^* would be in error. However, the data of primary interest are from the "normal-excretion" group where the transfer to milk is under conditions such that linearity assumptions are reasonable.

The low-excretion data closely fit a lognormal distribution ($R^2 = 0.95$) as shown in Fig. 3. There was some difference between the sample median (0.054 d L^{-1}) and the geometric mean (0.043 d L^{-1}) of the fitted lognormal distribution (Table 2). The excretion data, derived from the normal-excretion group, were much closer to a true lognormal distribution than was the low-excretion group, and were less varied as well. As shown in Table 2, the median (0.36 d L^{-1}) was nearly identical to the fitted geometric mean (0.37 d L^{-1}). The fitted GSD of the distribution of f_{hm}^* values for the normal-excretion group was 1.4 compared to 2.1 for the low-excretion group.

The range of estimates of the transfer coefficient, f_{hm}^* , within the normal-transfer group, may be a function of each woman's routine intake of dietary iodine—a quantity not known to the original investigators. Vermiglio et al. (1992) investigated the iodine concentration capacity of the mammary gland in an endemic goiter region in Sicily and showed that concentrations of iodine in milk from mothers living in an iodine sufficient region were about 30% greater than from mothers living in an iodine deficient region. However, the difference was not

Table 2. Summary statistics of estimates of f_{hm}^* , t_{max} and effective half-time from integral of fitted equations.

	Low-excretion group			Normal-excretion group			
	f_{hm}^* (d L ⁻¹)	t_{max} (h)	Effective half-time (h)	f_{hm}^* (d L ⁻¹)	t_{max} (h)	Effective half-time (h)	
Minimum	0.0078	1.9	1.8	Minimum	0.25	4.8	5.1
Maximum	0.15	52	45	Maximum	0.89	23	32
No. data points	14	14	14	No. data points	12	12	12
Mean	0.060	16	13	Mean	0.40	10	14
Median	0.054	8.7	6.6	Median	0.36	8.2	11
Std deviation	0.040	17	13	Std deviation	0.18	6.1	8.4
Std error	0.011	4.6	3.5	Std error	0.052	1.8	2.4
GM ^a	0.043	9.4	8.5	GM	0.37	9.0	12
GSD ^b	2.1	3.1	2.6	GSD	1.4	1.6	1.7
Weighted average	0.057	2.7	7.3	Weighted average	0.33	5.6	7.7
Std deviation of weighted average	0.021	1.6	0.70	Std deviation of weighted average	0.041	0.59	0.36

^a Fitted geometric mean (data fitted to a lognormal distribution).

^b Fitted geometric standard deviation (data fitted to a lognormal distribution).

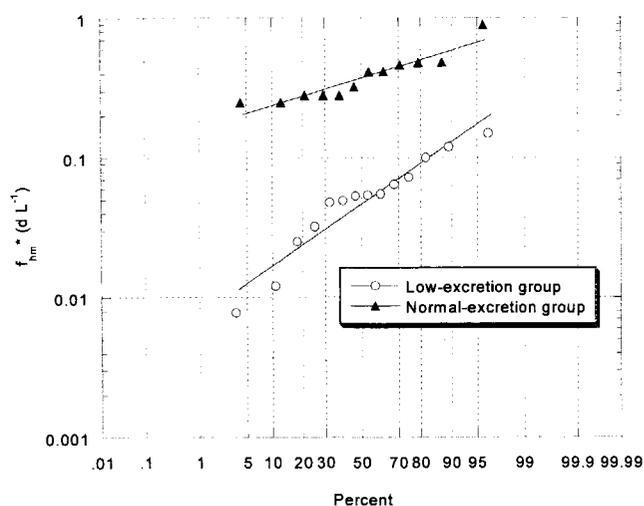


Fig. 3. Empirical cumulative distributions of f_{hm}^* values for ^{131}I transfer into human breast milk after separation of data into groups of “low-excretion” and “normal-excretion.”

statistically significant, possibly due to the small sample of only 11 women. Other data from those authors indicated that the percentage transfer of iodine into milk decreased with increasing daily iodine intake, suggesting the existence of a compensation mechanism to maintain relatively constant concentrations of iodine in their milk. Experiments with dairy cattle (Vandecasteele et al. 2000) and goats (Crout 2000), however, have shown that dietary levels of stable iodine can significantly affect the overall transfer of ^{131}I to milk. For both types of animals, modest increases (<10 \times) in dietary intakes of stable iodine led to increases in transfer of radioiodine to milk; however, large increases (20 to 100 \times) in stable iodine intakes led to decreases in the transfer of radioiodine to milk.

Either the medians or the weighted average values of Table 2 could serve as the best central estimates for

f_{hm}^* , t_{max} , and the effective half-time. In general, the weighted average would be the preferred value because such an average minimizes the variance. However, for the data sets used here, the variance of the estimated f_{hm}^* from one subject (subject #2 of Nurnberger and Lipscomb 1952) was much smaller than the others. Consequently, the weighted average (weights being the reciprocal of the variances) and the weighted standard deviation would be almost completely determined by the goodness of fit of the data for that subject to eqn (14). Because the variance for each subject was determined by propagating the errors of the coefficients of the regression model, the variances for a single subject would not reflect the variation among subjects—but rather the precision of that particular estimate. A similar situation exists for the estimates of t_{max} and effective half-time. For these reasons, the median or geometric mean value and their associated variance are good candidates for routine use rather than the weighted average and weighted standard deviation. Given that the data for f_{hm}^* , t_{max} , and effective half-time each closely fit a lognormal distribution (Figs. 3, 4, and 5), we recommend use of the fitted geometric means and geometric standard deviations (Table 2).

When the model of eqn (14) applies, the concentration at times $t > t_{max}$ is essentially governed by α_1 ; hence, the effective half-time following the time of peak concentration is approximately equal to $\ln(2) \alpha_1^{-1}$. Estimates of the effective half-time were obtained for each of the 26 subjects (Table 1). Consideration was given to the possibility that the low-excretion group would have associated effective half-times that were different than those of the normal-excretion group. The data suggested that effective half-time for the two groups were moderately different; the sample median values were 6.6 and 11.1 h for the low- and normal-excretion groups, respectively. Though there was some evidence that the normal-excretion group had longer effective half-times, the difference was not statistically significant. Similarly, the

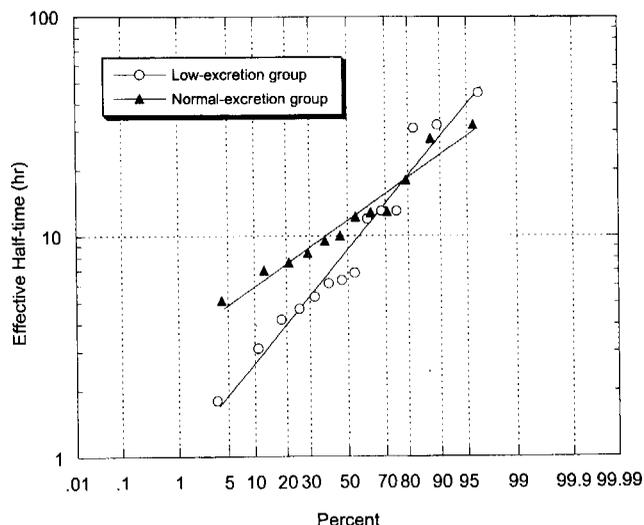


Fig. 4. Empirical cumulative distributions of calculated effective half-time (h) for ^{131}I in human breast milk (following time of peak concentration).

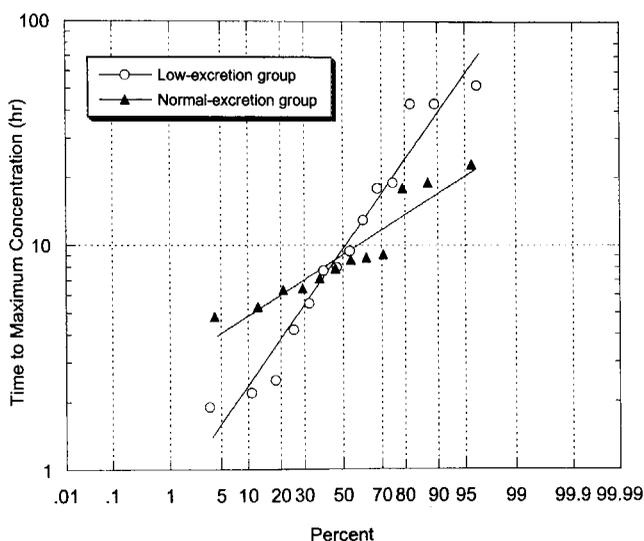


Fig. 5. Empirical cumulative distributions of calculated time (h) to maximum concentration of ^{131}I in human breast milk.

variation within each of the two groups appeared different (GSD of 2.6 for low-excretion group compared to 1.7 for normal-excretion group), though the difference was also not statistically different ($p > 0.05$) as determined by the squared ranks test for equal variances (a non-parametric replacement for the F-test, see Conover 1980). Cumulative probability distributions of the effective half-time estimates for the low- and normal-excretion groups are shown in Fig. 4. The values of effective half-time (Tables 1 and 2) compare closely with values reported by Mountford and Coakley (1989b) who summarized various parameters related to the excretion of radioisotopes in breast milk.

The times to maximum concentration, t_{max} , were estimated for each of the 26 subjects (Table 1) and summary statistics are presented for the two groups (Table 2 and Fig. 5). Consideration was given to the possibility that the low-excretion group would have associated t_{max} values that were greater than those of the normal-excretion group. Such a phenomenon seems plausible since the deiodination of the more complex chemical forms of iodine might require longer times. However, the median t_{max} for the low- and normal-excretion groups were almost identical, 8.7 and 8.2 h, respectively. The mean values appeared different, 16.4 and 10 h, respectively, though neither the medians nor means were significantly different. The variation of the t_{max} values within each of the two groups was significantly different (GSD of 3.1 and 1.6 for the low- and normal-excretion groups, respectively) ($p < 0.05$) as determined by the squared ranks test for equal variances. Apparently, the variety of chemical forms of iodine administered to the subjects, as well as differences in individual metabolism, led to substantial differences for the time to reach maximum milk concentration. That was particularly the case for the low-excretion group.

The finding that the effective half-times did not differ significantly between the low- and normal-excretion groups, appears to reflect the fact that the iodide, once assimilated into the breast milk, is excreted in an amount that is independent of its original chemical form. The indications that t_{max} differed between the low- and normal-excretion groups, even though the difference was not statistically significant, is consistent with the notion that the more complex forms require longer to metabolize before transfer into milk is possible.

CONCLUSION

We have presented a more generalized definition of the milk transfer coefficient by showing that regardless of whether intake is acute or constant, the milk transfer coefficient can be determined as the infinite time integral of $L(t)$, the time-dependent fraction of the input dosage excreted per liter of milk.

The presented geometric mean value of f_{hm}^* for the normal-excretion group, about 0.37 d L^{-1} (Table 2), is recommended for use in most radiological assessments of environmental releases of ^{131}I . It is our view that the group termed "normal-excretion" best represents women in the general public, in particular, in the United States or countries with similar diets and similar availability to stable iodine. The geometric standard deviation (GSD) of 1.4, while not a large variation, is a reflection of the different excretions by the women in the group. The variations presumably are a result of individual differences in metabolism, the chemical form of the administered radioiodine, the health status of each subject, and each woman's routine intake of dietary (stable) iodine. The GSD value can be used in a probabilistic dose assessment framework so that the distribution of the transfer coefficient is propagated with other variables into a distribution of possible doses to the milk drinker.

The principal explanation for the observed differences between the low- and normal-excretion groups is whether a blocking dose of stable iodine or complex chemical forms of radioiodine were administered. Dosages of stable iodine sufficient to block thyroid uptake also block or impair transfer into the mammary gland ostensibly by the sodium-symporter. Values of f_{hm}^* derived from the low-excretion group, with a sample median of about 0.054 d L^{-1} and a fitted geometric mean of 0.043 d L^{-1} , are recommended for use only when the subjects have continuously ingested very high iodide diets, when thyroid blocking doses of stable iodine or when unusual or complex chemical forms of radioiodine were administered.

The effective half-time of $\sim 12 \text{ h}$ and the time to maximum milk concentration of about $\sim 9 \text{ h}$ (both estimates from the normal-excretion group) are relevant for radiological assessments to the general public following an acute exposure. It is not possible to definitively state that these parameters were not influenced by medical conditions of the women studied. However, given the variety of medical conditions of the women under study, the transfer coefficient values are probably not overly biased towards any particular condition.

It is worth emphasizing that dosages of stable iodine administered to the mother for purposes of blocking uptake into the thyroid also protect the nursing infant. This mode of protection occurs as result of two related phenomena. First, saturation of the iodine symporter for the woman's breast occurs as a result of the thyroid blocking dosage; thus, transfer of radioactive iodine into the breast milk is inhibited. This action reduces, though does not eliminate, transfer of radioactive iodine to the nursing infant. In addition, the stable iodine that is transferred to the breast milk provides a blocking dosage to the infant's thyroid (Veall and Smith 1980), thus reducing the uptake of radioactive iodine by the infant.

Although it has been recognized for decades that radioiodine ingested by lactating women is readily transferred to breast milk, additional high quality data are still needed to properly and accurately characterize the potential excretion of ^{131}I into breast milk for women in the U.S. and in other countries.

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