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Quick Estimate of the Regulatory Virtually Safe Dose Based on the Maximum Tolerated Dose for Rodent Bioassays

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With a limited subset of National Cancer Institute/National Toxicology Program (NCI/NTP) bioassays, Gaylor (*Regul. Toxicol. Pharmacol.* 9, 101–108, 1989) showed that the regulatory virtually safe dose (VSD), corresponding to an estimated lifetime cancer risk of less than 10^{-6}, could be estimated within a factor of 10 simply by dividing the maximum tolerated dose (MTD), estimated from the results of a 90-day study, by 380,000. The purpose of this current study was to extend the analysis to all carcinogens in the Carcinogenic Potency Database (CPDB) utilizing the TD_{50} (average daily dose rate in mg/kg body wt/day that was estimated to halve the probability of remaining tumor-free at a specified tissue site throughout a 2-year study). Using the relationship between the upper bound on the low-dose slope (q^*) and the TD_{50} reported by Krewski *et al.* (*Risk Anal.* 13, 383–398, 1993) and the ratio of the maximum dose tested (Max-D)/TD_{50} obtained in our present analysis, an estimate of the regulatory VSD was given by the MTD/740,000, for NCI/NTP rodent carcinogens. This was about a factor of two lower than the limited analysis conducted by Gaylor. There was little difference when the chemicals were divided into mutagens and nonmutagens. Ninety-six percent (134 of the 139 NCI/NTP rodent carcinogens) of the regulatory VSDs calculated from the individual TD_{50}s obtained from the 2-year bioassays were within a factor of 10 of the MTD/740,000. Gold *et al.* (*Environ. Health Perspect.* 79, 259–272, 1989) investigated the distribution of the TD_{50} among "near-replicate" experiments (where the same chemical was tested more than once and was positive in the same strain, sex, and species by the same route). The distribution of TD_{50}s from near-replicate experiments is similar to the distribution of the Max-D/TD_{50}. Hence, the estimate of the regulatory VSD based on the Max-D/740,000, for NCI/NTP bioassays, is about as precise as the estimate obtained from a 2-year bioassay. This questions the advisability of conducting a 2-year bioassay for purposes of regulatory risk estimation. Since resources are available to test only a small fraction of chemicals to which humans are exposed, a preliminary estimate of the regulatory VSD can be useful in setting testing priorities. If the expected human exposure level is below the regulatory VSD estimated from the MTD, a chemical may be assigned low priority for testing in a 2-year bioassay. Based on previous work the FDA proposed a "threshold of regulation" of a dietary concentration of 0.5 ppb for all substances used in food-contact articles. The results of the present analysis could be used to make the procedure more chemical specific based upon an available MTD. The high correlation between the MTD and estimate of cancer potency (TD_{50}) can be exploited to provide a preliminary, hypothetical upper bound estimate of cancer risk for exposure to a chemical without conducting a 2-year animal bioassay. Thus, the expected level of human exposure relative to the MTD can be used to determine the priority for further research on a chemical, such as mechanistic studies.

INTRODUCTION

Rodent cancer tests are designed to maximize the chance of obtaining a positive result in a lifetime experiment with small numbers of animals (about 50 in each of 2 dose groups plus a control); the maximum tolerated dose (MTD) and half that dose are the standard dose levels used for that purpose in National Cancer Institute/National Toxicology Program (NCI/NTP) bioassays. This experimental design, with a narrow range of doses, was never intended to provide the information to quantitatively assess the risk to humans from chemical exposures at low doses. In current regulatory practice, however, the results of these high-dose rodent bioassays usually are the main source of data available to assess human cancer risk at exposure levels that may be hundreds of thousands of times lower than the MTD. Standard practice in risk assessment has been to estimate carcinogenic potency from bioassay data, and to obtain an upper bound on human risk (a hypothetical worst case) simply by making a linear extrapolation to the human exposure level, i.e., risk = potency × human

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exposure. The true risk may be zero at low doses. In recent years, an important, new emphasis has been placed on obtaining data on pharmacokinetics and the mechanism of action of a rodent carcinogen so that the dose–response, and therefore low-dose risk, can be more adequately assessed; however, such data are available on only a handful of chemicals.

Several recent analyses have pointed out the limited amount of information on cancer risks that is provided in bioassay data. In 1985, Bernstein *et al.* showed for an ideal two-group experiment that potency (TD_{50}) estimates, obtained from a statistically significant bioassay, are constrained to a narrow range (~32-fold) about the maximum dose tested in the absence of tumors in all dosed animals (which rarely occurs). The TD_{50} is the average daily dose rate in mg/kg body weight/day that was estimated to halve the probability of remaining tumor-free at a specified tissue site throughout a 2-year study. Later, Krewski *et al.* (1993) showed a similar result for q_1^* estimated from the linearized multistage model. TD_{50} estimates based on standard rodent bioassays must be close to the administered doses, regardless of whether the TD_{50} estimate is based on the one-stage, multistage, or Weibull model. Since cancer potency is inversely proportional to the TD_{50}, this narrow range of possible potency values from statistically significant tumor incidence rates in an experiment on a given chemical contrasts with the more than 10-million-fold range of potency values obtained across chemicals (Bernstein *et al.*, 1985). It also contrasts with the extrapolation that is required from the MTD administered to rodents to human exposure levels perhaps hundreds of thousands times lower.

Gaylor (1989) examined the constraints on potency estimation in an analysis of the distribution of the ratio MTD/(virtually safe dose), where the virtually safe dose (VSD) is an estimate of the dose corresponding to a lifetime tumor risk of no more than one in a million in rodents based on a multistage model and linear extrapolation. Using bioassays of the NCI/NTP, Gaylor (1989) examined 38 chemicals with positive results at the same tumor site in the same sex for both rats and mice. This could occur at more than one tumor site for a chemical. For this limited data set, the overall geometric mean of the ratio of the MTD to the VSD was 380,000, and 98% of the cases were within a factor of 10 of the mean. The striking implication of this fact is that the dose usually estimated by regulatory agencies to give less than one cancer in a million based on the linearized multistage model, can be approximated within a factor of 10 simply by dividing the 90-day MTD of a given rodent carcinogen by 380,000.

Based on the limited variation in the ratios of MTD/VSD, Gaylor (1989) proposed comparing estimates of human exposure to the MTD in rodents, for chemicals not previously tested in chronic bioassays, which would provide an approximation of the hypothetical "risk," as estimated by regulatory risk assessment. This approach involves making an exposure assessment at the outset. If the preliminary estimate of risk based on the MTD were below 10^{-7}, then even if the chemical were to test positive in a future carcinogenesis bioassay and allowing for an uncertainty factor of 10, the estimated risk would likely be below 10^{-6}, according to current regulatory risk assessment procedures. If the human exposure level is within a factor of 1000 of the MTD, an environmental contaminant which is carcinogenic in the rodent bioassay is likely to provide unacceptably high cancer risk estimates by current risk assessment techniques. In such cases, emphasis should be placed on generating data on pharmacokinetics and mechanisms of carcinogenic activity.

The purpose of this paper is to extend the previous analysis of the ratio MTD/potency and the preliminary estimation of a regulatory VSD to all rodent carcinogens in the Carcinogenic Potency Database (CPDB) of Gold *et al.* (1984, 1986, 1987a, 1990, 1993). If the ratio for nearly all chemicals is within a factor of 10 of the geometric mean, then it is reasonable to assume that this procedure will generally produce a standard, hypothetical risk estimate for a given human exposure that would be similar to that which would be obtained in a regulatory risk assessment for a rodent carcinogen, based on a 2-year bioassay. In order to approximate the procedure used in regulatory policy, we will select for each chemical the most potent TD_{50} among the target sites, based on tumor incidence data. We will examine the distribution of the MTD/TD_{50} ratio separately for the standard NCI/NTP bioassay whose protocols are similar to one another, and the bioassays in the general literature which vary in terms of the number of dose groups, the range of doses tested, and the experiment length, as well as in the number of strains, sexes, and species tested. If the new results are similar to those of Gaylor's earlier analysis (as would be expected because of the constraints on potency estimation), then this provides further evidence that it might be reasonable to use this approach in regulatory policy as a preliminary estimate of a VSD. Since resources are available to test only a small fraction of the chemicals to which humans are exposed, such a preliminary estimate may be useful for setting priorities for which chemicals to test in cancer bioassays or to conduct mechanistic studies. Although such a preliminary estimate of the VSD may lack validity for the true human risk, since rodent bioassay data are so limited, and the validity of linear extrapolation to low dose is generally not known for a given chemical, it would nonetheless be a close approximation to what is currently used in regulatory policy as a "risk estimate." Additionally, a preliminary estimate of the VSD could be used to identify specific chemicals that would not be of regulatory concern because their VSD would be higher than the levels to which humans are exposed, e.g., chemicals

that might migrate to food from packaging materials or leach out of medical devices.

METHODS

This study examines the relationship between the maximum dose tested (Max-D), which is the MTD, based on 90-day experiments, for NCI/NTP studies, and carcinogenic potency measured by the TD_{50} (average daily dose rate in mg/kg body wt/day that would halve the probability of remaining tumor-free throughout a 2-year study). The TD_{50} was readily available from the CPDB (Gold *et al.*, 1984, 1986, 1987a, 1990, and 1993). The data used were from two sources: (1) NCI/NTP chronic bioassays that were evaluated as "positive" in NCI studies prior to 1979, or having "clear" or "some" evidence of carcinogenicity in later studies, and (2) non-NCI/NTP (literature) bioassays which were considered positive by the authors of the publication and exhibited a statistically significant positive dose–response of $P < 0.05$ (two-tailed). Experiments were considered only if the chemical was administered for at least 18 months with the termination of the study after 21 months. A total of 139 NCI/NTP chemicals and 178 literature chemicals satisfied the above conditions.

The TD_{50} was calculated from crude summary data of tumor incidence by $(P - P_0)/(1 - P_0) = 1 - \exp(-\beta \cdot TD_{50}) = 0.5$, where β was the estimated one-hit parameter and P and P_0 were the proportions of animals that developed a specific tumor type in a dosed group and control animals, respectively, over the duration of the study. Summary data were used here because they are typically used in risk assessments for regulatory purposes. A calculation based on summary data ignores the age (time) at which death with tumor occurred, which seldom was given in literature publications. Summary data do not consider the effects of differential survival, i.e., different numbers of animals at risk across dose groups, during the duration of a study. Time-to-tumor data are available for NCI/NTP studies and do permit adjustments for the effects of intercurrent mortality as described by Peto *et al.* (1984). Assuming all tumors are rapidly fatal, the time-to-tumor TD_{50} values are reported in the CPDB for NCI/NTP bioassays and in Gold *et al.* (1989). Our results for NCI/NTP chemicals are similar if lifetable TD_{50} values are used (not shown).

As in the CPDB, when there was a significant departure from linearity in the dose–response with downward curvature, the high-dose data were dropped from the calculation of cancer potency (TD_{50}), but the Max-D was retained as the largest dose used in the bioassay. In the CPDB, for studies that were shorter or longer than the standard 2-year bioassay by a factor of f, the TD_{50} values were multiplied by the factor f^2. Since Max-D/TD_{50} ratios are unitless, it does not matter whether dose was expressed on a body weight or surface area basis, or as concentration in food or water.

Regulatory policy generally considers the most sensitive tumor site in a rodent bioassay for a chemical unless there is information that the site is not relevant for humans. Hence, the smallest TD_{50} (most potent) among target sites from positive experiments was selected, without regard to sex, strain, or species. For the Max-D/TD_{50} ratio, the Max-D is the highest dose tested in that experiment.

RATIO OF Max-D TO TD_{50}

A summary of the ratios of the Max-D to the most sensitive tumor site was compiled for 139 rodent carcinogens in NCI/NTP bioassays and for 178 rodent carcinogens reported in the general literature (Table 1). The chemicals were further subdivided as to whether they were mutagenic in *Salmonella*. For example, among the 77 mutagenic rodent carcinogens tested by the NCI/NTP, the geometric mean of the Max-D/TD_{50} ratios was 0.919. That is, the TD_{50} tended to be slightly larger than the Max-D. In this chemical subgroup, the ratio of the Max-D/TD_{50} varied by more than a factor of 10 from the mean (0.919) for only three chemicals, the lowest ratio was 0.078 and the largest was 11.7 (Table 2).

The somewhat larger ratio for mutagens compared to nonmutagens, particularly in the literature studies, indicates lower values of the TD_{50} relative to the Max-D. That is, as expected, mutagens tend to have greater carcinogenic potency relative to their Max-D than nonmutagens, suggesting higher tumor yields.

The larger ratios of literature chemicals compared to NCI/NTP, for both mutagens and nonmutagens, indicate that, in general, literature chemicals are more potent, relative to the Max-D. This may reflect differences and variation in experimental designs in the literature, e.g., the number of animals, number of dose groups, or the range of doses tested.

Only 14 of the 317 Max-D/TD_{50} ratios varied by more than a factor of 10 from their subgroup geometric means (Tables 1 and 2). That is, the TD_{50} was within a factor of 10 of the Max-D/(geometric mean) for 96% of the rodent carcinogens. Deviant ratios occurred at a variety of tissue sites. Of the four NCI/NTP studies with high ratios, all had maximum average adult body weights (prior to the growth of tumors) less than 80% of the control animals, indicating that the Max-D was too high. Since all of these extreme cases were reported in 1978 or 1979, there have not been any NCI/NTP studies since 1979 in which the Max-D/TD_{50} ratio differed from the geometric mean by more than a factor of 10. Six of the seven largest ratios had a high-dose tumor incidence that was less than the incidence at a lower dose. When this occurred, the high-dose data were not used in the calculation of the TD_{50}. Thus, the high dose used to estimate the TD_{50} was not the Max-

TABLE 1

Ratios of Max-D/TD_{50} Based on Summary Tumor Incidence Data for the Most Sensitive Tumor Site for Animal Carcinogens (Exposure Time ≥18 Months and Experiment Duration ≥21 Months)

Data category	Number	Max D/TD_{50}				Geometric mean	Number extreme[a]
		Lowest	5 percentile	95 percentile	Highest		
Mutagens							
NCI/NTP	77	0.078	0.140	6.12	11.7	0.919	3
Literature	64	0.078	0.174	7.43	34.8	1.46	4
Nonmutagens							
NCI/NTP	60	0.110	0.120	3.59	12.3	0.764	1
Literature	49	0.051	0.174	4.36	8.0	0.951	2
All chemicals[b]							
NCI/NTP	139	0.078	0.122	5.74	12.3	0.850	5
Literature	178	0.051	0.172	7.32	34.8	1.170	8

[a] Vary more than 10-fold from the geometric mean.
[b] Includes chemicals for which the mutagenicity status is unknown.

D, and the Max-D/TD_{50} ratio was artificially inflated. This plateau in the dose–response with high tumor yields is uncommon in rodent bioassays (Bernstein *et al.*, 1985). All of the seven lowest ratios had a low tumor incidence (Table 2). Four of these cases probably achieved statistical significance by combining data from both sexes, which is the only way that results were published.

QUICK ESTIMATE OF THE REGULATORY VIRTUALLY SAFE DOSE

Bernstein *et al.* (1985) demonstrated for NTP-type studies that the estimate of the TD_{50} for rodent carcinogens is restricted to a range of a factor of 32 about the Max-D, i.e., a factor of $\sqrt{32} = 5.7$ above and below its geometric mean, assuming that TD_{50} is log-normally distributed. For a similar analysis based on estimation of the upper limit of the low-dose slope, q_1^*, for the multistage model, Krewski *et al.* (1993) observed a 95% prediction interval of a factor of 8.4 about the mean estimate of q_1^* based only on the Max-D. Their analysis considered a less-restricted group of chemicals than Bernstein *et al.* (1985) and included experiments from the general literature as well as NCI/NTP. Whether based on the theoretical calculation of Bernstein *et al.* (1985) or the variation in experimental results ob-

TABLE 2

Ratios of Max-D/TD_{50} Based on Summary Tumor Incidence Data That Differ from Their Mean Ratio by More than a Factor of 10

Data category	Chemical	Species	Sex	Max-D/ TD_{50} ratio	Summary tumor incidence	Curve[a]
Mutagens (NCI/NTP)	2-Amino-4-nitrophenol[b]	Rats	Male	0.078	0/50, 1/50, 3/50	*
	4,4′-Thiodianiline[b]	Rats	Male	9.62	4/14, 33/35, 23/35	\
	1,2-Dibromo-3-chloropropane[b]	Rats	Male	11.72	0/50, 40/50, 39/49	\
Mutagens (literature)	Hydrogen peroxide[b]	Mice	Both	0.078	0/98, 1/101, 5/99	*
	Benzo(*a*)pyrene[b]	Rats	Both	0.112	3/64, 10/64	
	Phenylglycidyl ether	Rats	Male	0.133	1/90, 0/90, 9/90	*
	N-Nitrosodiethanolamine[b]	Rats	Male	34.8	0/88, 7/72, 43/72, 33/36, 32/36, 31/36	\
Nonmutagens (NCI/NTP)	4-Chloro-*o*-toluidine.*HCl*[b]	Mice	Female	12.3	1/20, 43/50, 39/50	\
Nonmutagens (literature)	*o*-Toluenesulfanamine[b]	Rats	Both	0.050	0/76, 3/76, 5/76	*
	Saccharin, sodium[b]	Rats	Male	0.064	0/36, 3/38	
Overall[c] (NCI/NTP)	1,2-Dibromoethane	Rats	Male	8.78	0/50, 39/50, 41/50	\
Overall[c] (literature)	3-Nitro-3-hexene	Rats	Both	0.075	0/100, 6/100, 11/100	*
	2-Acetylaminofluorene	Rats	Male	12.5	0/30, 3/29, 26/28, 23/23	*
	Vinyl bromide	Rats	Female	17.9	1/144, 10/120, 50/120, 61/120, 41/120	\

[a] Curve: "*", consistent with linearity; "\", significant departure from linearity, downward curvature.
[b] This chemical is also an extreme for the overall dataset.
[c] Overall includes mutagens and nonmutagens, as well as chemicals for which there is no mutagenicity evaluation. 1,2-Dibromoethane and 2-acetylaminofluorene are mutagens, but are not extremes in the mutagens-only dataset due to different geometric means.

served by Krewski *et al.* (1993) and in our present study, there is a limited range of TD_{50} or q_1^* values, relative to the Max-D, obtained from chronic bioassays. That is, for rodent carcinogens, potency can generally be estimated within a factor of 10 based only on the Max-D, without conducting an expensive 2-year bioassay.

The regulatory approach for estimating upper limits on low-dose cancer risk is

$$\begin{pmatrix}\text{Upper limit}\\ \text{on risk}\end{pmatrix} = \begin{pmatrix}\text{Upper limit on}\\ \text{low dose slope}\end{pmatrix} \times \begin{pmatrix}\text{human}\\ \text{dose}\end{pmatrix}$$

$$= q_1^* \times \text{dose}$$

Defining a virtually safe dose as the dose with a risk of less than 10^{-6}

$$10^{-6} = q_1^* \times (\text{VSD})$$

$$\text{VSD} = 10^{-6}/q_1^*. \quad (1)$$

Using summary tumor data from 191 carcinogens in the CPDB, Krewski *et al.* (1993) obtained for the TD_{50} estimated with the one-stage model

$$\log \text{TD}_{50} = -0.07 + 1.04 \log \text{Max-D} \quad (2)$$

and for q_1^* from the multistage model

$$\log q_1^* = 0.01 - 1.05 \log \text{Max-D}. \quad (3)$$

From Eq. (2)

$$\log \text{Max-D} = \frac{\log \text{TD}_{50} + 0.07}{1.04}.$$

Substituting this result into Eq. (3)

$$\log q_1^* = 0.01 - 1.05\left[\frac{\log \text{TD}_{50} + 0.07}{1.04}\right]$$

$$\log[q_1^* \cdot \text{TD}_{50}^{1.01}] = -0.06.$$

Since $TD_{50}^{1.01}$ is approximately equal to TD_{50}

$$q_1^* = \frac{0.87}{\text{TD}_{50}}.$$

Substituting this result into Eq. (1)

$$\text{VSD} = \frac{10^{-6} \times \text{TD}_{50}}{0.87}. \quad (4)$$

For NCI/NTP data we obtained for the geometric mean of all chemicals (Table 1)

$$\frac{\text{Max-D}}{\text{TD}_{50}} = 0.850 \quad \text{or} \quad \text{TD}_{50} = \frac{\text{Max-D}}{0.850}.$$

Substituting this result into Eq. (4) gives

$$\text{VSD} = \frac{10^{-6} \times \text{Max-D}}{0.87 \times 0.850} = \frac{\text{Max-D}}{740{,}000},$$

where Max-D = MTD for NCI/NTP bioassays.

DISCUSSION

Without data on mechanism of action for a given chemical, the true risk of cancer at low dose is highly uncertain, even for rats or mice. The standard risk assessment methodology provides a hypothetical, upper limit on risk, but the true risk may be zero. Our analysis does not attempt to provide a better estimate of risk based on bioassay data. Rather, because Max-D and carcinogenic potency are highly correlated, an approximation of the risk value generated by regulatory agencies can be obtained by using the Max-D as a surrogate for the TD_{50}, and then making the usual linear extrapolation to 10^{-6} risk. We find that the TD_{50} is within a factor of 10 of the Max-D for 98% of NCI/NTP rodent carcinogens and within a factor of 4 for 78%. Results are similar for the general literature, and for mutagens and nonmutagens in each data set.

Earlier analyses on variation in potency estimation when the same chemical is tested more than once and positive provide a baseline of comparison for judging whether the variation in Max-D/TD_{50} is much larger. If variation in potency estimates from two different experiments of the same chemical are similar to variation in the ratio of Max-D/TD_{50}, then confidence is provided in the use of the Max-D as a surrogate for the TD_{50}. Gold *et al.* (1989, Table 3) reported the distribution of the least to the most potent TD_{50} among "near-replicate" experiments, where the same chemical was tested more than once in the same strain, sex, and species by the same route and was positive in more than one test. Among all carcinogens in each species, Gold *et al.* (1989, Table 3) reported that the distribution of the ratio of least to most potent TD_{50} across experiments for a chemical is similar to that of near-replicates. The distribution of the carcinogenic potency ($1/TD_{50}$) from near-replicate experiments is similar to the distribution of Max-D/TD_{50} across chemicals. Hence, one would not expect much reduction in the uncertainty of a TD_{50} estimate based on a bioassay compared to the TD_{50} estimate based on the Max-D. Additionally, Zeise *et al.* (1984) noted that a relationship between cancer potency and the LD_{50} (acute dose that produces

50% mortality) could be used to obtain a crude estimate of tumor risk for rodent carcinogens. Further, Bernstein *et al.* (1985) observed that the lower confidence limit on the TD_{50} of a negative bioassay generally lies within the range of statistically significant TD_{50}s. On the basis of these analyses, it is reasonable to consider a preliminary estimate of the VSD based upon the Max-D for untested chemicals.

Gaylor (1989) gave the result VSD = MTD/380,000 for NCI/NTP-type bioassays. That result was based on a smaller number of cases than the present analysis and was restricted to chemicals with concordant target tissue sites in the same sex of both rats and mice. Multiple Max-D/VSD ratios from a single experiment were included if there was more than one target site. In the present analysis, which uses a larger number of chemicals and adopts the typical regulatory approach of selecting the most sensitive target site for a chemical, the divisor is a factor of 2 larger: VSD = MTD/740,000 for NCI/NTP-type bioassays.

The value of the VSD = MTD/740,000 is estimated to be within a factor of 10 of the VSD that would be obtained for a rodent carcinogen based on a 2-year NCI/NTP chronic bioassay. Since cancer potency estimates from different experiments of the same chemical also can vary up to a factor of 10 from their geometric mean, there may be little gain in precision by conducting a 2-year bioassay for quantitative risk estimation. Without the bioassay, the MTD can reasonably be used as a surrogate for estimating potency. To be consistent with regulatory policy, the minimum MTD in either rats or mice would be used. In order to prioritize chemicals for regulatory attention, an assessment of human exposure levels becomes critical at the outset. If the human exposure were estimated to be small relative to the VSD derived from the MTD, there may be little value in conducting a chronic 2-year study because the estimate of risk would be low regardless of the results of a bioassay. On the other hand, if the human exposure is large relative to the VSD and there is a high probability that the chemical may be a rodent carcinogen, caution for use of the chemical might be raised without conducting a 2-year bioassay. In such cases, research effort and funding might better be directed toward providing biological information on the mechanism of action so that a better assessment can be made of the risk at prevailing or expected exposures.

The U.S. Food and Drug Administration (1993) proposed a procedure for determining when the likelihood or extent of migration to food, of a substance used in a food-contact article, is so trivial as not to require regulation of the substance as a food additive. Of particular concern for lifetime exposures of substances at low doses was the potential for the development of cancer. The dietary concentration chosen as the "threshold of regulation" would have to be low enough to ensure that the public health was protected, even in the event that a substance exempted from regulation as a food additive was later found to be a carcinogen. Based in large part on analyses conducted by Rulis (1986, 1989, 1992), a dietary concentration of 0.5 ppb was proposed as the threshold of regulation for substances used in food-contact articles. Based on the range of carcinogenic potencies observed in 477 known animal carcinogens from the CPDB, and using conservative linear low-dose extrapolation, many chemicals would be estimated to pose less than a one in a million lifetime risk if present in the total daily diet at 0.5 ppb (Rulis, 1992). This is equivalent to a TD_{50} of 6.25 mg/kg body wt/day.

Rather than setting a single dietary concentration for the threshold of regulation of all substances, the results of the present analysis could be used to make the procedure more chemical specific. For rodent carcinogens, our analysis shows that on the average the VSD corresponding to a lifetime cancer risk of less than 10^{-6} was equal to the MTD/740,000. If, e.g., the MTD for a substance, as determined in a 90-day study, is 10,000 ppm, then the VSD is estimated to be 10,000/740,000 = 14 ppb in the total diet. If the MTD for a chemical were 100 ppm, then the threshold of regulation would be 0.14 ppb. Thus, the procedure based on the MTD would set different levels for the threshold of regulation for substances depending upon toxicity, whereas in the Rulis procedure a single threshold of regulation would be applied to all chemicals.

Regardless of the ultimate application, the high correlation between the MTD based upon a 90-day study and the estimate of cancer potency (TD_{50}) can be exploited to provide a preliminary, hypothetical upper-bound estimate of cancer risk for exposure to a chemical, without conducting a 2-year bioassay. Thus, the expected level of human exposure relative to the MTD can be used to set priorities for further study of a chemical.

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