REGULATORY TOXICOLOGY AND PHARMACOLOGY **28,** 222–225 (1998)
ARTICLE NO. RT981258

Regulatory Cancer Risk Assessment Based on a Quick Estimate of a Benchmark Dose Derived from the Maximum Tolerated Dose[1]

David W. Gaylor* and Lois Swirsky Gold†

*National Center for Toxicological Research, U.S. Food and Drug Administration, Jefferson, Arkansas 72079; and
†Lawrence Berkeley National Laboratory and University of California at Berkeley, Berkeley, California 94720

Received February 9, 1998

The proposed U.S. Environmental Protection Agency carcinogen risk assessment guidelines employ a benchmark dose as a point of departure (POD) for low-dose risk assessment. If information on the carcinogenic mode of action for a chemical supports a nonlinear dose–response curve below the POD, a margin-of-exposure ratio between the POD and anticipated human exposure would be considered. The POD would be divided by uncertainty (safety) factors to arrive at a reference dose that is likely to produce no, or at most negligible, cancer risk for humans. If nonlinearity below the POD is not supported by sufficient evidence, then linear extrapolation from the incidence at the POD to zero would be used for low-dose cancer risk estimation. The carcinogen guidelines suggest that the lower 95% confidence limit on the dose estimated to produce an excess of tumors in 10% of the animals (LTD_{10}) be used for the POD. Due to the relatively narrow range of doses in 2-year rodent bioassays and the limited range of statistically significant tumor incidence rates, the estimate of the LTD_{10} obtained from 2-year bioassays is constrained to a relatively narrow range of values. Because of this constraint, a simple, quick, and relatively precise determination of the LTD_{10} can be obtained by the maximum tolerated dose (MTD) divided by 7. All that is needed is a 90-day study to establish the MTD. It is shown that the LTD_{10} determined by this relatively easy procedure is generally within a factor of 10 of the LTD_{10} that would be estimated using tumor incidence rates from 2-year bioassays. Estimates of cancer potency from replicated 2-year bioassays, and hence estimates of cancer risk, have been show to vary by a factor of 4 around a median value. Thus, there may be little gain in precision of cancer risk estimates derived from a 2-year bioassay, compared to the estimate based on the MTD from a 90-day study. If the anticipated human exposure were estimated to be small relative to the MTD/7 = LTD_{10}, there may be little value in conducting a chronic 2-year study in rodents because the estimate of cancer risk would be low regardless of the results of a 2-year bioassay. Linear extrapolation to a risk of less than 1 in 100,000 and use of an uncertainty factor, e.g., of 10,000, would give the same regulatory "safe dose." Linear extrapolation to a virtually safe dose associated with a cancer risk estimate of less than one in a million would be 10 times lower than the reference dose based on the LTD_{10}/10,000.

INTRODUCTION

The proposed U.S. Environment Protection Agency carcinogen risk assessment guidelines (1996) employ a benchmark dose as a point of departure (POD) for low-dose risk assessment. For cancer the benchmark dose is defined as the dose with a low incidence rate of excess tumors above background, in the range of 1 to 10%, that generally can be estimated from rodent bioassay data. In contrast to a safety assessment based on a no-observed-adverse-effect level (NOAEL), a benchmark dose is estimated for a specified incidence rate, utilizes all of the dose–response data in its determination, and considers the variation in experimental data. A benchmark dose associated with an estimable excess tumor rate of 10%, i.e., tumorigenic dose for 10% of the animals (TD_{10}), has been proposed (EPA, 1996) unless data are adequate to estimate lower incidence rates. The TD_{10} can generally be estimated with little or no extrapolation. A lower confidence limit (LTD_{10}) has been proposed as the POD for low-dose cancer risk assessment to assure that the excess tumor rate is not likely to be greater than 10% (EPA, 1996). When available, physiologically based pharmacokinetic (PBPK) data would be used for more accurate dose estimation to the target tissue.

If data on the mode of action of a chemical support a nonlinear dose–response curve below the LTD_{10}, then the LTD_{10} could be divided by uncertainty (safety) factors to arrive at a reference dose (Barnes and Dourson, 1988) that is likely to produce no, or at most negligible, cancer risk for humans. If human exposure

[1] The opinions expressed are solely those of the authors and not necessarily those of the U.S. Food and Drug Administration.

data are available, then the margin-of-exposure (MOE) ratio between the LTD_{10} and anticipated human exposure would indicate the margin of safety (EPA, 1996). If there is insufficient evidence to support nonlinearity, then linear extrapolation from the LTD_{10} to zero would be used to estimate the risk of cancer (EPA, 1996). The proposed policy requires a biomarker for carcinogenicity and thus may require a long-term animal bioassay to establish the POD, e.g., the LTD_{10}, for low-dose cancer risk assessment.

A number of investigators (Zeise *et al.*, 1984; Bernstein *et al.*, 1985; Gaylor, 1989; Metzer *et al.*, 1989; Travis *et al.*, 1990; Krewski *et al.*, 1993; Freedman *et al.*, 1993; Gaylor and Gold, 1995) have discussed the observed correlation between carcinogenic potency estimated from bioassay data and chemical toxicity in rodents, including the maximum tolerated dose (MTD) as a measure of toxicity. Due to the limited dose range and limited range of significant tumor incidence rates possible from 2-year rodent bioassays, the estimate of cancer potency from a 2-year is constrained to a relatively narrow range (Bernstein *et al.*, 1985). This constraint can be exploited to provide a quick estimate of a lower limit on a benchmark dose estimated to produce a specified excess tumor incidence, e.g., 10%, based on only the MTD from a 90-day study. This lower limit may be used as a POD for cancer risk assessment; for chemicals that might be animal carcinogens at the MTD, without conducting a 2-year bioassay. Without information on the mechanism of carcinogenic action for a chemical, the true risk of cancer at low doses is highly uncertain, even for rats and mice. The standard risk assessment methodology provides a hypothetical upper limit on cancer risk, but the true risk may be zero. Since estimates of risk are constrained by the standard experimental design, it is demonstrated that an approximation of the risk value generated by regulatory agencies can be obtained based on the 90-day MTD without conducting a 2-year bioassay. This paper provides a procedure that may provide sufficient information to forego conducting a 2-year bioassay when using a benchmark dose approach for cancer risk assessment.

METHODS

Based on a retrospective study of the outcomes of 139 chemicals tested by the National Toxicology Program (NTP) that demonstrated evidence of carcinogenicity in rodents, Gaylor and Gold (1995) indicate that without conducting a 2-year bioassay, based upon the MTD derived from a 90-day study, the carcinogenic potency can be estimated within a factor of 10 of the potency estimated from fitting the multistage model to tumor incidence data from a 2-year study. An explanation for the ability to estimate the potency from the MTD is that the 2-year bioassay permits only a relatively narrow range of statistically significant excess tumor incidence over a narrow range of doses (Bernstein *et al.*, 1985).

Gaylor and Gold (1995) indicate that a quick estimate of the regulatory virtually safe dose (VSD) corresponding to a cancer risk of less than 10^{-6} is generally within a factor of 10 of the MTD/740,000. In standard regulatory risk assessment methodology, the upper limit on low-dose cancer risk has been estimated from the upper limit on the estimate of the cancer potency factor (q_1^*) times the dose

$$10^{-6} = q_1^* \cdot \frac{\text{MTD}}{740{,}000}$$

giving $q_1^* = 0.74/\text{MTD}$ for animal carcinogens. Hence, a quick estimate of the LTD_{10} is provided by the linear term of the multistage model where the excess probability (P) of tumors is estimated to be

$$P = 1 - \exp(q_1^* \cdot \text{dose}).$$

Setting $P = 0.1$ gives

$$0.1 = 1 - \exp\left[-\frac{0.74}{\text{MTD}} \cdot \text{LTD}_{10}\right]$$

and

$$\text{LTD}_{10} = \text{MTD}/7.$$

The regulatory virtually safe dose (VSD) estimated to be associated with a risk of less than 10^{-6} used for regulatory purposes would be the $LTD_{10}/100{,}000 = \text{MTD}/700{,}000$, which is similar to the result given by Gaylor and Gold (1995) for the VSD based on the linearized multistage model. This derivation of the LTD_{10} based on the MTD from a 90-day study is likely to be within a factor of 10 of the LTD_{10} obtained from fitting a multistage model to tumor incidence results from a 2-year bioassay.

Thus, a simple and relatively quick determination of the POD for cancer risk assessment is provided by the MTD/7 from a 90-day study. The proposed carcinogen risk assessment guidelines (EPA, 1996) indicate that a POD could be determined from a biomarker for carcinogenicity, e.g., cell proliferation, and need not be based on tumor incidence data. If a nonlinear dose–response below the POD is expected, then the margin of exposure between the MTD/7 and anticipated human exposure level would be considered. Barnes and Dourson (1988) discuss the use of uncertainty (safety) factors to establish, within an order of magnitude, a reference dose presumed to have zero, or at most, negligible levels of risk. If nonlinearity cannot be substantiated, then the default would be linear extrapolation to zero from the POD, which is similar to the risk estimate using the linearized multistage model (Table 1).

TABLE 1
Cancer Risk Assessment without Conducting a 2-Year Bioassay

Approach to risk assessment	Estimated regulatory "safe dose"
Low-dose linear extrapolation based on the multistage model[a]	
Risk $< 10^{-6}$	MTD[b]/740,000
Risk $< 10^{-5}$	MTD/74,000
Risk $< 10^{-4}$	MTD/7,400
Benchmark dose POD = LTD_{10}[c] with linear extrapolation	
Risk $< 10^{-6}$	MTD/700,000
Risk $< 10^{-5}$	MTD/70,000
Risk $< 10^{-4}$	MTD/7,000
Reference dose for nonlinear dose–response curve based on uncertainty factors	
LTD_{10}/1000[d]	MTD/7,000
LTD_{10}/10,000[e]	MTD/70,000

[a] Gaylor and Gold (1995).
[b] MTD, maximum tolerated dose (high dose in rodent test).
[c] LTD_{10}, lower confidence limit on dose to produce 10% of rodents with tumors.
[d] Combined uncertainty factors of 10 for animal to human extrapolation, 10 for sensitive humans, and 10 since the LTD_{10} represents a low-observed-adverse-effect level (Barnes and Dourson, 1988).
[e] Additional uncertainty factor of 10 would be considered to account for possible extra sensitivity of children per the Food Quality Protection Act of 1996 or because of the severity of cancer even from low doses (Renwick, 1995; Schwartz, 1995).

A summary of these shortcut cancer risk assessment procedures, that do not require a 2-year bioassay, is given in Table 1. Both linear extrapolation and uncertainty factors proportionately reduce a tumor dose in a similar manner (Gaylor, 1983). The difference in the regulatory "safe dose," if any, for the two approaches depends on the level of risk selected and the number and magnitude of uncertainty factors selected.

DISCUSSION

The 2-year bioassay used by the NTP was designed to maximize the chance of detecting an increase in tumor incidence with a fixed number of animals by using the MTD. Typically, 50 animals of each sex of mice and rats are dosed at the MTD, MTD/2, and recently at the MTD/4, along with unexposed controls. This experimental design with a narrow range of doses near the MTD was never intended to quantitatively assess the risk to humans from exposures at much lower doses. However, the results from these high-dose rodent bioassays generally have been the primary source of data used to estimate human cancer risk for chemical exposures at low doses.

Gold *et al.* (1987) investigated the reproducibility of results from "near-replicate" 2-year bioassays where the same chemical was tested more than once in the same strain and sex by the same route of exposure. Based on those results, Gaylor *et al.* (1993) demonstrate that 95% confidence limit for the reproducibility of near-replicate bioassay results is approximately a factor of 4. Since the overall variability for the estimate of the LTD_{10} based on the 90-day MTD is about a factor of 10, a relatively small gain in the precision of the quantitative cancer risk estimate is accomplished by actually conducting a 2-year bioassay.

The approach in this paper can be used in conjunction with a human exposure assessment at the outset to determine priorities for further actions. If the margin of exposure between the POD (MTD/7) and anticipated human exposure is large enough or if estimates of risk based on linear extrapolation from the MTD/7 to zero are small enough, even if the chemical were to be a rodent carcinogen the cancer risk estimate could be deemed negligible without conducting a 2-year bioassay. If the human exposure level were not sufficiently below the POD (MTD/7), then a chemical which is carcinogenic in a rodent bioassay would likely provide unacceptably high cancer risk estimates. Since resources are available to test only a fraction of the chemicals to which humans are exposed, the shortcut procedure proposed here should be useful for selecting options for further actions.

The value of the ratio, MTD/7, is expected to be within a factor of 10 of the LTD_{10} (POD) that would be obtained for a rodent carcinogen from a 2-year NCI/NTP chronic bioassay. Since cancer potency estimates from different strains of animals for the same chemical also can vary up to a factor of about 10 from their geometric mean (Gaylor *et al.*, 1993), there may be little gain in the precision of cancer risk estimates by conducting a 2-year bioassay. 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. 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 LTD_{10} derived from the MTD, there might 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 were not sufficiently below the LTD_{10} and there were 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 be better directed toward providing biological information on the mechanism of carcinogenic action so that a better assessment can be made of the risk at prevailing or expected exposures.

Using the benchmark dose approach of the proposed carcinogen risk assessment guidelines (EPA, 1996), the

dose estimated from the LTD_{10} divided, e.g., by a 10,000-fold uncertainty factor is similar to the dose with an estimated risk of less than 10^{-5} using a linear model. This dose is 10 times higher than the virtually safe dose corresponding to an estimated risk of less than 10^{-6}.

CONCLUSIONS

A reasonably precise estimator of the LTD_{10} can be obtained simply by dividing the MTD by 7 without conducting a 2-year bioassay. Based on anticipated human exposures, this POD dose may provide sufficient information for low-dose cancer risk estimation or for setting an RfD to forego conducting a 2-year bioassay. If the human exposure were estimated to be sufficiently small relative to the LTD_{10} derived from the MTD, there might be little value in conducting a chronic 2-year study because the estimated risk would be low regardless of the results of the chronic bioassay. On the other hand, if the human exposure were not sufficiently below the LTD_{10}, caution might be raised without conducting a 2-year bioassay.

Regardless of the ultimate application, the relationship between the MTD based upon a 90-day study and the estimate of cancer potency can be exploited to provide a preliminary, hypothetical upper-bound estimate of cancer risk for exposure to a chemical or provide an RfD, without conducting a 2-year bioassay.

REFERENCES

Barnes, D. G., and Dourson, M. (1988). Reference dose (RfD): Description and use in health risk assessments. *Regul. Toxicol. Pharmacol.* **8,** 471–486.

Bernstein, L., Gold, L. S., Ames, B. N., Pike, M. C., and Hoel, D. G. (1985). Some autologous aspects of the comparison of carcinogenic potency in rats and mice. *Fundam. Appl. Toxicol.* **5,** 79–87.

Food Quality Protection Act (1996). Public Law 104–170. U. S. Code of Federal Regulations. Washington, D. C.

Freedman, D. A., Gold, L. S., and Slone, T. H. (1993). How tautological are inter-species correlations of carcinogenic potency? *Risk Anal.* **13,** 265–272.

Gaylor, D. W. (1989). Preliminary estimate of the virtually safe dose for tumors obtained from the maximum tolerated dose. *Regul. Toxicol. Pharmacol.* **9,** 101–108.

Gaylor, D. W. (1983). The use of safety factors for controlling risk. *J. Toxicol. Environ. Health* **11,** 329–336.

Gaylor, D. W., Chen, J. J., and Sheehan, D. M. (1993). Uncertainty in cancer risk estimates. *Risk Anal.* **13,** 149–154.

Gaylor, D. W., and Gold, L. S. (1995). Quick estimate of the regulatory virtually safe dose based on the maximum tolerated dose for rodent bioassays. *Regul. Toxicol. Pharmacol.* **22,** 57–63

Gold, L. S., Wright, C., Bernstein, L., and deVeciana, M. (1987). Reproducibility of results in "near-replicate" carcinogenesis bioassays. *J. Natl. Cancer Inst.* **78,** 1149–1158.

Krewski, D., Gaylor, D. W., Soms, A. P., and Szyszkowicz, M. (1993). An overview of the report "Correlation between carcinogenic potency and the maximum tolerated dose: Implications for risk assessment." *Risk Anal.* **13,** 383–398.

Metzer, B., Crouch, E., and Wilson, R. (1989). On the relationship between carcinogenicity and acute toxicity. *Risk Anal.* **9,** 169–177.

Renwick, A. G. (1995). The use of an additional safety or uncertainty factor for nature of toxicity in the estimation of acceptable daily intake and tolerable daily intake values. *Regul. Toxicol. Pharmacol.* **22,** 250–261.

Schwartz, C. S. (1995). A semiquantitative method for selection of safety factors in establishing OELs for pharmaceutical compounds. *Hum. Ecol. Risk Assess.* **1,** 527–543.

Travis, C. C., Richter Pack, S. A., Saulsbury, A. W., and Yambert, M. W. (1990). Prediction of carcinogenic potency from toxicological data. *Mutat. Res.* **241,** 21–36.

U.S. Environmental Protection Agency (1996). Proposed guidelines for carcinogen risk assessment: Notice. *Fed. Reg.* **61**(79), 17995–18011.

Zeise, L., Wilson, R., and Crouch, E. (1984). Use of acute toxicity to estimate carcinogenic risk. *Risk Anal.* **4,** 187–199.