Controlled Clinical Trials

Tukey (*1*), in discussing multiple analyses as data accumulate during a controlled clinical trial, leaves the reader with the impression that repeated "looks at the data" invariably require that a larger level of significance be assigned to the overall procedure. In making this point, he cites the work of Armitage. McPherson, and Rowe (*2*) in which only procedures with a fixed upper bound on the sample size are considered.

Tukey fails to mention that there is a general method that can be applied to such sampling procedures which permits continual testing of the data without affecting the overall level of significance. The method in question is based on the idea that, as soon as sufficient data have been accumulated so that the outcome of the test to be performed on the completed data set is certain, then the inference provided by the test can be made immediately at the nominal level of significance [see (*3*), pg. 719]. Applications of this (early stopping) idea have been described in the binomial case (*4*), the Wilcoxon two-sample test (*3*, *5*), and in several other tests (*6*).

The early stopping idea can be applied in principle to a number of statistical tests currently employed in clinical trials; however, the complex design and actual conduct of some trials may make it difficult at the outset to define appropriate stopping rules of any kind. When this idea can be applied the resulting savings in observations (and time) will vary with the statistical test and the pattern of entry of patients into study. Savings may be quite substantial for the Wilcoxon test but are only modest in the binomial case; in general, savings tend to decrease as the length of time during which patients enter study increases. Use of the early stopping idea ensures that the inference made at the time of stopping will be the same as that which would be made if the trial continued to its planned conclusion, that is, the inference based on the outcome in all the patients. In this respect the procedure differs from the type suggested by Tukey (*7*) for which it is possible for the two inferences in question to be conflicting.

Tukey asserts "Once our clinical trial has accumulated favorable evidence for an innovation up to whatever level of significance . . . physicians judge appropriate for action, we cannot, ethically, continue the trial . . . *just to measure the improvement* with greater precision." We think this statement might be broadened to assert that a clinical trial should be stopped as soon as the final inference is a foregone conclusion. Application of the early stopping idea is a method of continually testing this possibility.

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19 January 1978; revised 5 September 1978

I do not disagree with Alling, Halperin, and Ware. I should be glad to see such "curtailed sampling" applied. "Stopping when you know what the answer will be" is very different from "stopping when the answer looks good."

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6 October 1978

Models for Carcinogenic Risk Assessment

Cornfield (*1*) presents a simple kinetic model for carcinogensis that could lead to a threshold. Cornfield shows that such a threshold depends on the existence of at least one irreversible completely protective reaction in the carcinogenic process. He then asserts that this model has as much theoretical justification as others and therefore should be used as part of the safety evaluation procedures for governmental regulatory agencies. We do not argue against the possible existence of such thresholds, nor do we disagree with the potential utility of models based on pharmacokinetics; however, we wish to point out inadequacies in Cornfield's derivation and express our concern with the implications of this article on the assessment of low-exposure carcinogenic risk.

Cornfield's threshold model implicitly requires either instantaneous deactivation of the toxic substance at the target site or complete deactivation before reaching the target. His derivation of this model is based on a steady-state solution to a process in which an irreversible deactivation reaction takes place in vivo. We agree that in the presence of a single exposure, when the amount of the toxic substance is less than the amount of the deactivator, then all of the toxic substance will eventually be converted to the deactivated substance. However, this process will take time to reach equilibrium and, under Cornfield's assumption of proportionality between dose and the probability of a carcinogenic response, if any activated complex ever reaches the target site, a threshold will not exist. We also call attention to the unrealistic assumption of a single exposure implicit in Cornfield's derivation. The primary concern with environmental carcinogens is with situations of either continuous exposure, such as agents in the air we breathe, or with repeated exposures from food or water additives or contaminants. A more realistic model would require continuous production and degradation of deactivator and substrate as well as continuous or repeated exposure to the toxic substance.

Cornfield's model assumes the existence of a single threshold applicable to each member of the exposed population. However, thresholds may vary over time within an individual as well as varying among individuals in the population. This variability of thresholds is most important from a regulatory point of view since all members of a heterogeneous population must be protected at all times. His establishment of a single "population threshold" is of little value to a regulatory agency that must consider the lowest threshold for an individual over his exposure period, as well as the lowest thresholds in the entire population.

Answers to the questions raised by Cornfield are likely to be obtained through basic research in carcinogenic pathways and pharmacokinetics and not by examining limited animal bioassay experiments. With limitations in the current knowledge of carcinogenesis, we see no alternatives for the prudent regulator but to base his decisions on the assumption of no threshold.

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6 March 1978

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Cornfield (*1*) suggests the use of equations describing the metabolic activation and inactivation of carcinogens as a possible useful device for arriving at permissible threshold doses. Such a procedure might well have efficacy, but only if the calculated threshold doses applied only to the very sharply defined conditions of the experiments used to obtain them. These conditions usually involve repeated dosing with the tested substance, but data obtained in this way do not take into account the fact that two distinct processes can be involved in carcinogenesis: initiation and promotion. Thus, at doses of carcinogen too low in themselves to cause cancer, tumors may yet be formed providing that promotion subsequently occurs through action of other substances which also are noncarcinogenic alone. Such promotion can begin at very long times after initiation (*1*, *2*). Some examples of promotion applicable to man may be the increased tumor incidence associated with unsaturated fats, phenobarbital, and tobacco tars.

Complete carcinogens both initiate and promote; therefore the terms "no observable level" (NOEL) or "acceptable daily intake" (ADI) apply to the combined effects. However, the very low levels of carcinogens (some being natural metabolites) which suffice for initiation suggest that most people already have initiated cells and that major carcinogenic risks may come from promoting agents in environmental pollutants, tobacco smoke, foods, drugs, and cosmetics.

In this context, the NOEL and ADI may have to be scaled down to much lower levels, above which tumors may be promoted by environmental agents over a time interval equal to some significant part of a human lifetime. In the case of dibenzanthracene, an initiator with very little promoting activity (*2*), the NOEL and ADI would be quite high but would be vastly lowered when followed by promoting agents. In the methylcholanthrene example given by Cornfield, it is not known whether the calculated parameters apply to initiation or promotion, or both, although the intriguing comparison of tumor incidences obtained with metabolic activation-inactivation equations and the probit-log dose curve (*1*) suggests that Cornfield's approach may be a useful one. Even if this turned out to be the case, the myriad of instances in which these processes are effected by different agents and in different time frames would seem to render carcinogenic risk assessment entirely unreliable by techniques now used except as applied to strictly defined conditions of dosage with complete carcinogens. In other cases, two-stage initiation-promotion experiments (*2*, *3*) may have to be carried out to obtain estimates of permissible doses and exposure times (each being dependent on the other) for both initiators and promoters. The problem is "mind-boggling" because of the enormous number of possible combinations of initiating agents, promoting agents, and time frames. An urgent step may be to determine acceptable exposure levels and times for various environmental promoting agents under the assumption that people already have initiated cells. Cornfield's approach may have utility here provided that a similar mathematical formulation applies to promoting agents.

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Cornfield (*1*) proposed a kinetic model for dose-related induction of cancer that included free carcinogenic substance, metabolite, and a deactivator compound. Cornfield showed that for a special case of his model there is a threshold dose below which there is no carcinogenic risk, and suggested that statistical procedures based on this threshold model might find a place in safety evaluation procedures. However, the conditions necessary for a threshold include a perfect instantaneous deactivation, a situation unlikely to occur in nature. Cornfield himself showed that whenever the deactivation reaction is reversible, the threshold disappears and the carcinogenic response increases linearly with dose at low doses. This is true regardless of how slowly the reverse reaction occurs. Furthermore, even in the unlikely situation of perfect deactivation, an otherwise realistic model should still imply low-dose linearity, because some elapsed time (probably infinite) would be required for the perfect deactivation to be completed. Thus Cornfield's threshold model is unstable since a slight perturbation of the model in the direction of realism does away entirely with the threshold and leads to low-dose linearity.

There are other plausible models for the induction and promotion of cancer which imply that cancer risk will increase linearly with dose at low doses (*2*); however, I do not know of a mechanism that would lead to a more conservative dose-response relationship at low dose, such as the risk increasing as the square root of the dose. Consequently, when one is estimating cancer risks from an environmental carcinogen, it would seem reasonable to base such estimates on a mathematical model that encompassed low-dose linearity unless, of course, the mechanism through which the carcinogen operated was sufficiently understood that low-dose linearity could be conclusively ruled out. Once the principle of low-dose linearity is accepted, the range of uncertainty for estimates of additional risk at doses near zero is greatly narrowed (*3*). This is because the disagreement between upper statistical confidence intervals for extra risk based on two reasonable models that incorporate low-dose linearity is typically less than an order of magnitude.

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3 January 1978; revised 5 September 1978

I applaude the following statement of Tukey (*1*): "Many of us are convinced, by what seems to me to be very strong evidence, that the only source of reliable evidence . . . is that obtained from well-planned, and carefully conducted randomized . . . double-blind clinical trials." It is just this kind of evidence, stemming from laboratory experiments with lower organisms, that causes me to express reservations regarding the article by Cornfield (*2*). Cornfield's article is concerned with the difficulties experienced by the regulatory agencies, for example, the Food and Drug Administration (FDA), in determining what is occasionally called "virtually safe" exposures to possibly carcinogenic agents. Although Cornfield recognizes (*2*, p. 698) that "regulatory decisions must be made, and formalisms with more theoretical or experimental support . . . should be preferred to those with less," it seems to me that his own approach ignores certain important experimental findings.

One item which I miss in Cornfield's approach is the recognition that the response to a carcinogenic agent depends on the rate of exposure. For the radioactive agents the priority for the study of the so-called dose-rate effects appears to belong to Upton (*3*). A review (*4*) indicates that important dose-rate effects exist also for certain chemical carcinogens.

Another item that I miss in Cornfield's approach is the phenomenon of synergisms. The importance of this phenomenon is dramatically emphasized by the title of a recent symposium (March 1977) organized by the Biology Division of Oak Ridge National Laboratory, namely, Symposium on Mechanisms of Tumor Promotion and Co-Carcinogenesis. The subjects discussed at that conference are marked by tale-telling terms: initiator, tumor promoter, and inhibitor. In view of these developments, the problem of the FDA regarding some chemicals C_1, C_2, C_3 is not limited to their possible carcinogenic effects when administered singly, but also in combinations such as C_1 and C_2, C_1 and C_2 and C_3. Statistical methodologies relating to such problems—the so-called multiple comparison problems—were summarized by Miller, first in a monograph and then in the *Journal of the American Statistical Association* (*5*). However, the problem of an optimal methodology does not appear to have been solved and represents an inspiring challenge to mathematical statisticians [see (*6*)]

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Risk assessment at very low doses of carcinogen is faced with the problem of whether or not a threshold dose is zero. In biochemical terms the question is whether the molecular fate of a carcinogen is proportional or disproportional to dose. Cornfield (*1*) concluded that with decreasing dose a relatively higher percentage of carcinogen (C in our Fig. 1), its activated derivative (or derivatives) (C*), and relevant DNA adduct (or adducts) (C*-DNA) would be eliminated(C_1^0) by the cells' protective mechanisms

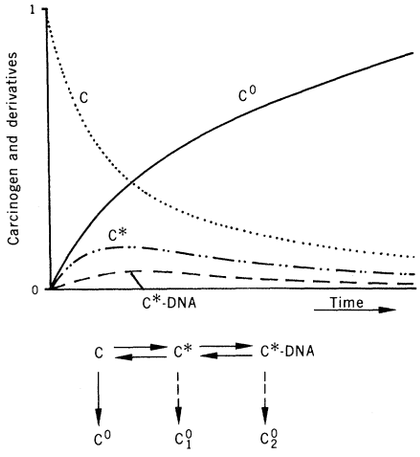

Fig. 1. Amount of carcinogen and its derivatives as a function of time following a single application.

(deactivation, DNA repair, for example) leading to zero relevant interaction at very low doses. Only if the protective mechanisms were saturated or overwhelmed by sheer numbers of carcinogenic molecules would carcinogenically relevant interactions occur.

In Cornfields's model all the reactions in which carcinogen participates are considered to be reversible, except at least one irreversible protective reaction. Furthermore, the model is analyzed for steady-state condition and apparently, though this is not mentioned, for a single-dose exposure. In such a system in steady state the amount of C*-DNA will be zero and all carcinogen will have been detoxified.

It should be noted that in this model, steady state is, by definition, only reached if all carcinogen is converted irreversibly into detoxified products C^0, and that before this state is reached the amount of C*-DNA will have been greater than zero (Fig. 1). Now, as long as C*-DNA, the promutagenic lesion, is present it has a certain chance of being fixed genetically (during DNA synthesis or by misrepair) leading to an irreversible effect (mutation) (*2*). Moreover, the less reversible the pertinent reactions are, the longer will C*-DNA exist in higher concentration and the greater is the chance that an irreversible effect will ensue. In fact, the reactions in which chemical carcinogens are involved can be considered as virtually irreversible; persistent C*-DNA lesions have also been identified (*3*).

If carcinogen is applied continuously to this model, the amount of C*-DNA will be greater than zero under steady-state conditions.

Cornfield's "hockey-stick" kinetics (zero carcinogenic response at low doses, followed by a steep increase at higher doses, linear plot) do not correspond to the results of calculations of Gehring (*4*) on C*-DNA formation as a function of dose [see figure 5 in (*4*)]. According to Gehring, the normalized quantity (ratio between C*-DNA and dose) is plotted against dose (on a double logarithmic scale). The horizontal part of that curve in the low-dose range thus indicates a direct proportionality between the amount of C*-DNA formed and the dose.

The demonstration by Cornfield of fit of the Bryan and Shimkin data to his model is unconvincing because the data may be inappropriate for this purpose and the model contains too many free parameters. Since tumor incidence is a function of dose rate and time (*5*), tumor responses should be measured at a fixed time for all doses employed if a kinetically meaningful result is to be obtained. In the above experiments, however, the mean latent period was 2.4 months for the highest and 6.96 months for the lowest effective dose group.

We therefore maintain that Cornfield's data do not support threshold kinetics in chemical carcinogenesis.

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9 January 1978; revised 28 August 1978

An author cannot escape complete responsibility for misinterpretation of his writings, but I nevertheless suggest that only a misreading of my article could have led to characterizing the model given there as a threshold model. The threshold holds for the special case of a steady-state model in which the deactivation reaction is irreversible and will not hold, as several of the correspondents have pointed out, when the time course of the reaction is taken into account. But once the irreversibility assumption is relaxed, as it is in the page-

long section entitled "An expanded kinetic model," the threshold argument can no longer be sustained even under the steady-state assumption, as the article explicitly states. The basic conclusion of the article, which is reached only after the irreversibility assumption is dropped—that the probability of a response rises rapidly only after the dose administered saturates the deactivation system and that estimation of the saturation dose might find a place in safety evaluation procedures—is not therefore dependent on the existence of a threshold. Similarly, the charge of Brown *et al.* that my model "assumes the existence of a single threshold applicable to each member of the exposed population" appears to have overlooked the statement in my article: "Since we are here interested in qualitative implications, and not detailed statistical procedures, I shall not consider the modifications of Eq. 10 required to allow for animal variation in parameter values."

The allegation that the single exposure model is unrealistic has perhaps made insufficient allowance for the identity of the dose-response implications of single and repeated exposure models. The latter does highlight, however, the essentially trivial contribution of the pre-steady-state period to total exposure. If the variables of the formulation are interpreted as time rates, sustained at the steady state by constant infusions of dose, substrate, and deactivator with degradation by first-order kinetics of all five variables by excretion, repair, or other mechanisms, the model goes through unaltered. Thus, if the rates of infusion of substrate, deactivator, and dose are, respectively, S, T, and D, the positive rate constants for degradation of substrate, deactivator, toxin-substrate complex, toxin-deactivator complex, and dose are κ_s, κ_t, κ_x, κ_y, and κ_d, and the notation is otherwise that of my article, the steady-state equations are:

$$S - \kappa_s s - kds + k_- x = 0$$

$$T - \kappa_t t - k^* dt + k_-^* y = 0$$

$$D - \kappa_d d - kds + k_- x - k^* dt + k_-^* y = 0$$

$$kds - k_- x - \kappa_x x = 0$$

$$k^* dt - k_-^* y - \kappa_y y = 0$$

Eliminating d, s, and t we obtain equations 7 and 8 of my article with new variables x' and y' replacing x and y, where $x' = \kappa_x x$, $y' = \kappa_y y$, k is replaced by $\kappa_d \kappa_s (k_- + \kappa_x)/k\kappa_x$, k^* by $\kappa_d \kappa_t (k_-^* + \kappa_y)/k\kappa_y$, and $P = x'/S$. The functions relating P and D are thus identical for single and repeated exposure models. (Note that the last term of equation 8 of my article should be $K^* y$ and not $K^* x$.)

Table 1.

Percentage in diet	Number responding/ number exposed
0	0/127
0.02	0/48
0.20	0/48
0.75	1/91
1.5	2/91
2.0	12/48

The low-dose linearity of various models and, in particular, that of Crump *et al.*, needs to be interpreted in the light of his own question, "How linear is 'linear'?" (*1*). For the pharmacokinetic model considered in my article the second derivative of the dose-response curve at low dose levels can be positive even for $K^* > 0$, and the work of Gehring and Blau, cited in my article, shows that for typical values of rate constants it is indeed positive. When agents for which the kinetics are not known lead to a markedly convex dose-response curve, as for the kidney tumor response to nitrolotriacetic acid (*2*), it might therefore appear reasonable to use a model with this property. But the upper confidence limits in Crump's model, cited in his reference 3, are often equivalent to those yielded by the one-hit curve, which is concave. That this can make a profound difference in estimates of allowable exposure, is illustrated by calculations using the NTA results, given in Table 1. The lower 97.5 percent confidence limit on the dose leading to a lifetime probability of response of 10^{-4} is 0.7×10^{-3} percent in the diet if one uses the Crump model, 1.3×10^{-3} percent if one uses the one-hit model but 0.9 percent in the diet, or 1000-fold higher, if one uses a multihit model, which, like the pharmacokinetic model, does not impose low-dose concavity on data which are markedly convex (*3*).

That a model can be "too" linear is also suggested by the remark of Hoel *et al.* (*4*) that "applying the linear model to all chemicals could result in the elimination of many chemicals from our environment on the grounds that they present an unacceptable carcinogenic risk even though there was no experimental evidence of their carcinogenicity." In the words of the Scientific Committee of the Food Safety Council (SCFSC), of which I am a member, "what is required is a procedure which assumes low-dose linearity when data in the observable range suggest this, but rejects the assumption when the shape of the curve suggests that high doses have saturated the repair, protective or other mechanisms by which multi-cellular organisms cope with low doses—without, however, assuming the existence of unobservable population thresholds" (*5*, p. 117). The pharmacokinetic model described in my article should, after statistical implementation, provide such a procedure.

I agree with McGaughey that the problems that combination carcinogenesis can present to the regulator are "mind-boggling" in their complexity. The joint effects can be additive on the dose scale, in which case the dose-response curve at low doses must be presumed linear although not necessarily concave; they can be less than linear, or even antagonistic, all of which have been reported for different cases of combination carcinogenesis (see reference 24 in my article). A step in the direction of taking account of these complexities is suggested by the statement of the SCFSC "from the regulator's point of view it would appear as if additive joint effects are not so common as to be automatically assumed, but that when their existence, and hence low-dose linearity, is suspected, this existence should be investigated by appropriate factorial experimentation" (*5*, p. 113), but it is only a step.

The foregoing remarks also cover the comments of Neyman and of Scherer and Emmelot, except that I believe the last two authors misinterpret the dependence of latent period on dose in the Bryan-Shimkin experiments to imply that tumor incidence in that experiment did not refer to lifetime incidence, as it did. More generally, as Chand and Hoel (*6*) have shown, if median time to tumor is that function of dose found by Druckery, as cited by Scherer and Emmelot, and if the distribution around that median is lognormal, then tumor incidence measured at a fixed time is described by a probit-log-dose curve, as found by Bryan and Shimkin.

I fear that only faulty exposition on my part could have led even three correspondents to conclude that I was proposing a threshold model. But with this point and others clarified, is it too much to expect that they reexamine the article for possible positive content? The problem of low-dose risk assessment is too important and the scientific basis for it too slender for any of us to adopt immovable positions.

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23 October 1978

Atmospheric Carbon Dioxide in the 19th Century

In his study of $^{13}C/^{12}C$ ratios of tree rings, Stuiver (*1*) adds to a growing body of evidence that the biosphere as well as the combustion of fossil fuels may have contributed to the recent rise in atmospheric CO_2. He appears, however, to have misinterpreted 19th-century measurements of atmospheric CO_2 in finding that they support his deduction of an atmospheric CO_2 increase between 1850 and 1900.

From isotopic data and oceanic modeling considerations, Stuiver deduces that the atmosphere had a CO_2 content of only about 268 parts per million (ppm) in 1850, whereas the generally accepted value is about 290 ppm (*2*). In support of his deduction, Stuiver quotes a 19th-century "measurement" of 274 ± 5 ppm, which he attributes to Brown and Escombe (*3*). Actually, Brown and Escombe reported a mean of 294 ppm based on 92 observations which they made at Kew, England, between 1898 and 1901. The curiously low figure of 274 ppm appeared, however, in a review of 19th-century data published nearly four decades later by Callendar (*4*). Stuiver evidently relied on Callendar's value without examining the original publication.

At first glance, Callendar's value cannot be dismissed as an error, since he rejected some of Brown and Escombe's observations to arrive at a mean which he regarded as representative of the "free air of the North Atlantic region." Nevertheless, it seems highly unlikely that he arrived at a "representative" value of 274 ppm when all but 7 of Brown and Escombe's 92 measurements were higher than 274 ppm. Furthermore, in a second article (*5*), Callendar explained in detail how he obtained "representative" values by the use of weather maps. He reported then that 54 of Brown and Escombe's observations, during southwest to northwest winds, yield a mean of 286 ppm, while 20 observations, during southeast to northeast winds, yield a mean of 313 ppm. The latter mean very likely reflects urban contamination because of the proximity of Kew to the "great city" of London to the east, and should be rejected in establishing "free air" values. Air movements could not be definitely established for the remaining observations. Finally, in a still later article (*6*), Callendar quoted for Brown and Escombe a mean of 286 ppm, which he labeled a "preferred 19th century CO_2 average." Thus Callendar's reference to 274 ppm is probably a copy error or miscalculation which he later revised upward.

Actually, Stuiver's isotopic data and modeling considerations suggest that the annual mean CO_2 content of the air rose at nearly a constant rate from 268 ppm in 1850 to 312 ppm in 1950. A content near 290 ppm is thus indicated for 1900, in close accord with Brown and Escombe's observations.

But what do earlier historic observations tell us about a linear rise before 1900? Callendar's careful analysis (*5*) of 19th-century data suggests a steady content near 290 ppm. But all the data are of questionable accuracy, and data before 1870 are hopelessly unreliable. Thus, whether Stuiver's conclusions about the biosphere are correct will probably depend on the integrity of isotopic data and not on historic atmospheric CO_2 observations.

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8 June 1978

I fully agree with Keeling that the accuracy of the conclusions about anthropogenic biospheric carbon fluxes depend on the integrity of the isotopic data and not on historical atmospheric CO_2 observations.

By using ^{13}C and ^{14}C isotopic data, an atmospheric CO_2 content of 268 ppm was obtained for mid-19th-century air (*1*). One short paragraph in (*1*) was devoted to a comparison of this result with CO_2 contents measured during the last century. It was noted that most measured values were higher for the 19th century. For the quoted value of 274 ppm, ascribed to Brown and Escombe (*2*), I indeed relied on Callendar's article summarizing historical CO_2 measurements (*3*).

Brown and Escombe reported the measurement of 91 (not 92) samples. Several of these samples were contaminated by CO_2 from local sources. Perhaps one should attach major significance to lower values because these may represent the smallest possible additions. Brown and Escombe reported 15 samples with a CO_2 content below 280 ppm, of which one, at 243 ppm, is clearly anomalous. The others all fall in the range 265 to 280 ppm and average 274 ppm. Although I make no claim about the accuracy of those early measurements, these remarks illustrate that the 290-ppm value inferred from historical measurements should be considered with caution.

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