Chapter 14

Threshold of Regulation

Options for Handling Minimal Risk Situations

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The Food and Drug Administration (FDA), under the Federal Food, Drug, and Cosmetic Act, requires the premarket safety evaluation of new uses of food additives. The statute defines as additives even those substances that may inadvertently become components of food by migrating from food packaging, and provides no cutoff below which chemicals migrating in very low amounts may be considered exempt from petition requirements. It is clear, however, that at very low levels of migration the agency's expenditure of resources to regulate such materials may result in negligible public health gain. What is an appropriate level to define as a "threshold of regulation," below which no petition for a new use need be submitted and approved? FDA's development of a scientific basis for such a regulatory cutoff using risk assessment has spanned several years. One approach considered by FDA employs a statistical analysis of potencies of known chemical carcinogens. The present paper will examine options open to the agency in this potentially precedent-setting policy area.

Is there a basis for defining a "Threshold of Regulation" (T/R) to exempt substances under the Federal Food, Drug, and Cosmetic Act (the Act) from premarket regulatory requirements? Specifically, what situations involving extremely low exposure to food chemicals migrating to food from food-contact materials (e.g., components of food packaging materials, or food handling equipment, etc.) could be considered *de minimis* (*1*) under the statute, and thus would not require the submission of a food additive petition and a full-blown petition review by the Food and Drug Administration (FDA)? The agency has been developing answers to such questions over several years (*2-5*), and is now nearing a workable solution (*6*).

Since the passage of the 1958 Food Additives Amendment to the Act, FDA has often considered such questions in regard to so-called "indirect food additives" (food packaging and other food-contact materials that are not added directly to food but become components of food by virtue of unintended migration to food), particularly

when potential human exposure to such additives is extremely low and thus unlikely to produce any possible public health concern. The statute defines food additives, including the migrating indirect additives, quite broadly[1]. In particular it provides no exposure "floor" below which substances are not considered to be food additives and thus are exempt from premarket petition review and safety evaluation. Furthermore, the Delaney anticancer clause of the Act prohibits the use of any additive that has been shown to induce cancer in man or animal. (It is not intended that a T/R policy would be applicable to chemicals demonstrated to be carcinogenic.)

Until now the agency has lacked a policy under which to make T/R decisions in a consistent manner. Instead it has used a case-by-case approach. Since the 1958 amendment to the Act, FDA has written many letters exempting situations from food additive petition review because of the specific facts of a case. There are many examples of situations where the agency has deemed the minuscule human exposure to a chemical in question to be of no consequence and not a food additive concern under the Act. Representative examples might be the use of an adjuvant in the matrix of a food processing conveyor belt; a material used in nonfood-contact fixtures in a food processing plant; a colorant, polymerization catalyst, or other adjuvant, used at exceedingly low levels in a plastic food packaging material; etc.

Need for a Threshold-of-Regulation Policy

Today there is an increasing need for FDA to make decisions of the type described above more routinely, with greater consistency, and on a firmer scientific basis. It is also becoming more important for the agency to focus its limited resources more on issues of major public health impact and not to allow resources to be disproportionately focused on a myriad of minimal risk situations that are of negligible public health consequence. Yet present trends indicate that greater effort is in fact not always able to be expended on issues in direct proportion to their public health importance. Most of the food additive petitions reviewed by the agency are for food-contact substances (indirect food additives) rather than for direct food additives. Since 1958, FDA has reviewed and regulated an average of about 60 petitions per year for indirect additives, but only about 15 on average for direct food additives, color additives, and "generally recognized as safe" (GRAS) food ingredients. Even though indirect additive petitions are typically smaller and simpler to process than direct food additive petitions, the agency devotes over 40 percent of its petition review resources to the processing of indirect additive petitions. Some petitions are for such low-exposure uses of indirect additives that it may be legitimately questioned whether the safety decision results in any net measurable gain in public health protection. Yet the agency's formal review

[1]As has been amply noted previously, the Federal Food, Drug, and Cosmetics Act requires the premarket safety evaluation of all new uses of food additives. The statute, however, defines as additives even those substances that may become components of food by migrating from food packaging, and provides no cutoff below which chemicals migrating in very low amounts may be considered exempt from petition requirements.

mechanism for these petitions, including environmental impact considerations, legal reviews, and Federal Register publication, all operating under statutory time frames, must be fully engaged.

A T/R policy could help to alleviate this problem by providing a simpler alternative mechanism, apart from the full-dress petition review process, under which the agency could grant approvals for limited uses of a substance. Under such a policy any person could seek a T/R exemption from petition review for the proposed use of a given substance. The requestor would supply adequate information to identify the chemical in question, describe its proposed use, and provide limited data from which agency scientists could estimate the likely incremental human intake resulting from the proposed use. If, after reviewing the information, FDA decided to grant an exemption, it would issue a letter to the requestor and maintain a record of the decision in agency files. If the process were structured so as to permit decisions to be made in a short time compared to the time required for a full petition review, then the process would free resources for other more important issues. Of course, whether the net effect of this process on resources is helpful would depend on many considerations including the amount of current petition work actually diverted to the less arduous path, as well as any increase in petition submissions or requests for advisory opinions that are not now being sent to the agency from industry.

Somewhat paradoxically, instituting a T/R policy for indirect additives may, in some ways, actually represent a tightening of FDA requirements for indirect additives. First, it is the agency that would offer T/R exemptions to requestors; this is not thought of as a "do-it-yourself" exemption process. A request for an exemption need not be granted. Even if all nominal conditions were satisfied, FDA might decide not to exempt certain substances on the basis of knowledge of the chemical structures involved and the likelihood that those structures might be associated with high toxicity. Furthermore, current toxicological requirements for petitioned indirect additives presenting less than 50 parts per billion (ppb) dietary exposure consist, at minimum, of simply an acute feeding study and a literature search. A T/R level on the order of 1.0 ppb or lower, for example, would focus regulatory attention on a range of human exposures lower than 50 ppb. Users of indirect additives in applications resulting in dietary exposures of 10, 5, or 2 ppb or lower, under their *assumption* of *de minimis* status, would be encouraged to seek an agency opinion as to whether their application qualifies for an exemption from regulatory requirements. (In the initial stages, this might even result in a temporary increase in workload for the agency.)

During 1989, FDA conducted a Pilot Study to examine practical approaches to implementing a T/R policy. (The Study and its outcome have been described by Borodinsky (*7*). In that study, 35 T/R cases were examined at a total expenditure of about 120 person-hours of deliberation, or an average of 3.4 person-hours to reach a decision in each case. This is a considerable saving compared to the usual agency effort required to process a typical indirect food additive petition, which, although highly variable, may range from 250 to 500 person-hours on average.

Selection of a Threshold Level

A difficult issue in creating a T/R policy is the selection of an appropriate migration level to food or human dietary exposure level for the threshold. A simple solution might seem to be to arbitrarily pick a conservatively low level of migration to food from food-contact materials, for example, 25 or 50 ppb, and to define any situation with less migration to be below the threshold. This approach, however, is far from optimal. First, potential risk is related more closely to human dietary exposure than to migration. Setting a migration-based T/R level does not recognize this fact. Another approach would be to simply set the T/R level low enough to preclude any potential risk of toxicity from any chemical migrating into food, including ones of known high toxicity such as dioxin (TCDD). This approach, however, is not only unnecessarily conservative, but it would also require that the dietary intake level chosen as the threshold be set so low (femtogram levels in the case of TCDD) as to make such a policy useless. Not only is it unlikely that any materials used at such low levels would actually produce a technical effect in a food-contact material, but today's analytical measurements are insufficiently sensitive to routinely demonstrate the presence of the material below that level. Thus, in practice, no chemical would be able to pass such a threshold requirement.

Conversely, a level arbitrarily set too high would undermine the effect of the statute and perhaps create the possibility of unnecessary risk if the substance granted the exemption were to possess considerable toxicity.

To be relevant to potential human risk, the T/R level must be based on likely dietary intake from food, and not on migration. It also must be relevant to known toxic endpoints of chemicals at the level of intake, and as Schwartz has shown (*5*), it must be in the realm of present-day analytical capabilities. Because carcinogenesis occurs in animals at exposure levels generally lower than for most other types of toxic effects, a policy based on that toxic endpoint would provide a conservative measure of protection from almost all types of presumptive toxicity. For this reason FDA has considered that its T/R policy should use carcinogenesis as the basis for establishing the threshold (*2-4*). Such an approach is also consistent with the agency's established precedent for using upper-bound estimates of risk from carcinogenesis as a standard of negligible risk, in both its Sensitivity of the Method regulation for animal drugs (*8*) and its policy regarding Carcinogenic Impurities in Food Additives (*9,10*).

Use of Carcinogen Potencies to Establish a Threshold of Regulation

One approach to establishing a T/R level is to base that level on the degree to which presumptive carcinogenic risk may be ruled out, in the unlikely event that the compound is a carcinogen. FDA's approach to precluding potential carcinogenic risk makes use of potency data compiled from substances that have tested positive for carcinogenesis in animal feeding studies. Both the FDA (*2-4*) and others (*11-14*) have discussed this approach.

Carcinogen potencies are known to be lognormally distributed (Figure 1). From this distribution it has been shown (*2*) that the choice of a given exposure level for a

T/R excludes a probabilistically defined proportion of the area under the lognormal curve of potencies from producing dietary risk to humans above any chosen "Target Risk" level, so long as human exposure to the substance of concern does not exceed the T/R exposure level. The Target Risk level is that upper-bound level of presumptive lifetime risk deemed commensurate with negligible or *de minimis* risk, and is typically chosen to be 1×10^{-6} (*8-10*). Given this Target Risk and the range over which carcinogen potencies are known to be distributed, one may select a threshold level that provides adequate protection from presumptive carcinogenic risk in excess of the Target Risk.

In an earlier paper on this subject, a T/R level of 50 parts per trillion (ppt) was proposed for illustration (*2*) using the method described above. It was shown how that choice of T/R level is consistent with an 85 percent probability that an upper-bound risk of greater than 1×10^{-6} would be precluded for each exemption at that level, should the substance unexpectedly be a carcinogen. (Coupled with an assumed one-in-five probability of an untested chemical being a carcinogen, the choice of 50 ppt leaves a better than 97% probability that cancer risk will not exceed 1×10^{-6}.)

In fact, for any *range* of selected T/R levels there exists a *corresponding range* of probabilities that presumptive carcinogenic risk at some target risk level is precluded. These "Target Risk Avoidance Probabilities" correspond to areas under the lognormal curve of carcinogen potencies excluded by any given choice of T/R level. The relationship between these two variables is portrayed in Figure 2, which shows Target Risk Avoidance Probabilities as a function of the T/R level chosen. The shape of the curves in Figure 2 depends solely on the parameters that define the shape and position of the lognormal distribution of carcinogen potencies. Two curves from this author's work are portrayed in Figure 2, one corresponding to 343 carcinogens selected from the original data base compiled by Gold et al. (*2,15*) and the other, a more recent one using 477 carcinogens chosen from an updated Gold et al. database (*16,17*). The choice of 50 ppt as a T/R level is designated by Arrow "A" in Figure 2.

Schwartz has proposed a range of possible T/R levels between 100 ppt and 1 ppb (*5*). The lower bound for this range was justified on the basis of known diffusion coefficients for migrating species from polymeric food-contact materials, and represents a practical limit to current analytical capability for indirect food additives. At the upper limit (1 ppb) the target risk avoidance probability begins to exceed 50 percent. The range proposed by Schwartz is shown as the span between arrows "B" and "C" in Figure 2.

Recently, Munro et al. published a table of Target Risk Avoidance Probabilities (*see* Reference 11, Table 2) as well as parameters defining the lognormal potency curves for each of four carcinogen data sets they studied (*13*). Using their parameters, we have plotted in Figure 2 the Target Risk Avoidance Probabilities for two of their data sets, including the one they state to be of most relevance to the T/R problem. As can be seen from Figure 2, the Munro et al. analysis is in substantial agreement with the present analysis. Munro et al. argue that a dietary intake level as high as 1 ppb provides adequate protection from presumptive cancer risk, and that the level may be even higher, possibly as high as 10 to 15 ppb, if adequate data are available to preclude the genotoxicity of the chemical in question (*14*). The T/R level suggested by Munro

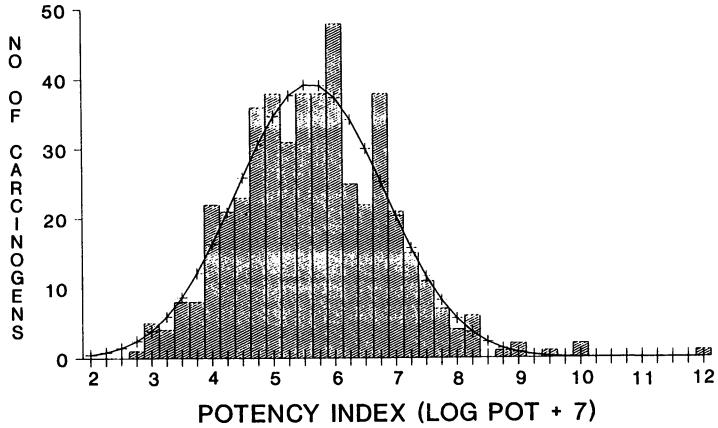

Figure 1. Probability distribution of carcinogen potencies based on the data base of Gold et al. (*15-17*) for 477 selected carcinogens.

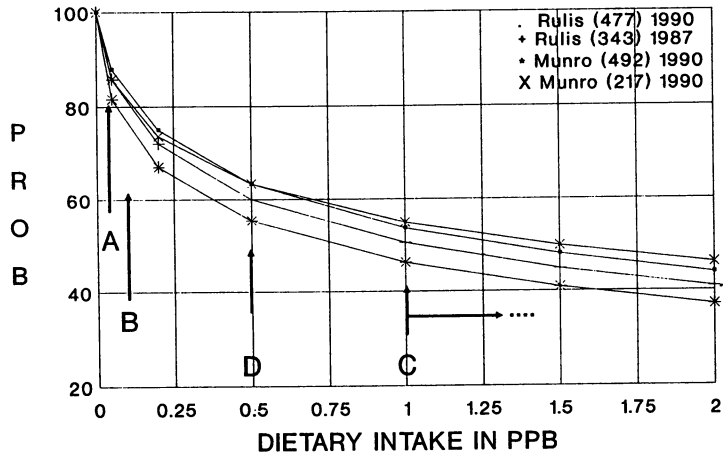

Figure 2. Target Risk Avoidance Probabilities as a function of human dietary intake. Data of Rulis (*2*) and Munro et al. (*11*). **Ordinate** represents the probability that presumptive upper-bound risk of carcinogenesis would not exceed 1×10^{-6} upon lifetime ingestion at the dietary level indicated on the abscissa. **Arrow A** corresponds to a T/R level of 50 ppt (*2*). **Arrows B and C** represent a range of possible T/R levels described by Schwartz (*5*). **Arrow C** and above corresponds to the proposed T/R level of Munro et al. (*11-14*). **Arrow D** corresponds to a T/R level of 0.5 ppb. Data set 1 (•) of Rulis is from an unpublished analysis of 477 carcinogens selected from the Gold et al. data base. Data set 2 (+) of Rulis is from a previously published analysis of 343 Gold et al. carcinogens. Data set 3 (*) of Munro et al. is from a set of 492 Gold et al. carcinogens. Data set 4 (X) is from a set of 217 carcinogens selected by Munro et al. to be the best representative set for the purposes of establishing a T/R level.

et al. is shown in Figure 2 as arrow "C" at 1 ppb with an indefinite span to the right of that level.

Taken together, the data of Figure 2 show that an upper-bound presumptive risk of carcinogenesis from lifetime dietary ingestion of a carcinogen at a level of 1 ppb will be less than 1×10^{-6} with roughly a 50 percent probability (Arrow C), while at lower dietary intakes it becomes increasingly probable that the potential risk will not exceed that target risk level. Recall that these "risks" are conjectural and not actuarial in any sense. They are upper-bound estimates derived from a highly conservative linear extrapolation of data from animal studies. Furthermore, it has been presumed that the chemical in question is in fact a carcinogen. This is not likely to be true for more than about one in perhaps three to five randomly selected compounds.

At the present time it appears that a T/R level on the order of 0.5 ppb (arrow "D" in Figure 2) may represent a reasonable balance between necessary conservatism and practical utility. In the absence of any detailed toxicological information about a compound, including genotoxicity information, this level provides adequate protection from presumptive carcinogenic risk, and is also within the realm of analytical measurability.

Summary and Conclusions

Several impelling considerations currently point to establishment of a T/R for food packaging materials. The 1979 Monsanto vs. Kennedy decision of the United States Court of Appeals reminded the agency of the Commissioner's limited exemption authority under the present statute. FDA has yet to formally delineate its understanding of the scope and application of that exemption authority. The Monsanto court decision provides both an opportunity and an impetus to move forward with a T/R policy. Furthermore, industry petitioners for new food additives deserve to have consistent and expeditious decisions about their products under regulatory authority of FDA. These decisions must also protect the public health. Regulatory agencies need to find more ways to employ the "principle of commensurate effort," under which they systematically devote their limited resources to issues in proportion to the likely net public benefit. Expeditious handling of a larger number of trivial or near trivial issues would allow more attention to be focused on the less numerous, yet more important, issues. These are all major concerns related to the T/R policy for indirect food additives under development at FDA.

Scientific analyses suggest that even if the toxicological endpoint of carcinogenesis is selected as the key factor in setting a T/R level for indirect food additives, a level can be set that is both practical from the analytical standpoint and fully protective of public health. A level of the order of 0.5 ppb may be a reasonable starting point for such a policy, lying as it does, midway in a range bounded by analytical limitations on one end and by increasing probability of presumptive toxicity on the other. Of course, FDA has not yet settled on a specific T/R level, nor for that matter does it have the specific considerations of a policy fully laid out. When the agency develops its approach to a point where outside opinion and independent review will be helpful, we intend to publish a proposal in the Federal Register and request public comment.

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