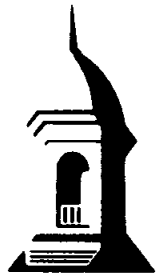
Risk Characterization for Food Additives and Contaminants

by
Josephine A. Mauskopf

Food Marketing Policy Center
Research Report No. 8



The University of Connecticut
Department of Agricultural Economics
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1. Introduction

The goal of risk characterization is to provide quantitative estimates of the health hazards associated with exposure to harmful substances or organisms in a form that is useful for risk management. For example, the results of a risk characterization might provide useful inputs for three types of risk management decisions made by government decision makers concerned with food safety:

- Determining whether health risks from exposure to specific food additives or contaminants are above or below acceptable levels
- Setting maximum permissible residue or contamination levels
- Choosing among alternative regulation or compliance monitoring options.

For all of these decisions it is important to have estimates of the health risks associated with the estimated exposure scenarios.

Risk characterization is usually listed as the fourth component of risk assessment, the first three components being hazard identification, exposure assessment, and dose- response modeling. Risk characterization for food additives or contaminants combines the information on likely health effects from the hazard identification with the exposure and dose-response estimates. The results of the risk characterization are estimates of: the size of individual lifetime risks for each likely health effect for different population subgroups; the size of the individual health risks each year after exposure for different population subgroups; and the expected number, severity, and timing of cases of the health effects in each population subgroup. Methods for performing the first three steps of the risk assessment process are the topic of extensive research and are continually being refined. However, although the risk characterization step has been performed for many hazardous substances, there has been very little attempt to develop a systematic methodology for this final and important step in risk assessment. A recent exception to this is Naugle *et al.* (1989).

The goal of this paper is to provide a framework for the development of a more rigorous methodology for risk characterization. Risk characterization can be subdivided into three related activities, derivation of point estimates for a single expo-

sure scenario, uncertainty analysis for these point estimates and the exposure scenario, and aggregation of point estimates and uncertainty for multiple exposure scenarios. For each of these activities, we present a methodological framework, review the methods commonly being used, and suggest ways in which these methods might be improved.

2. Point Estimates

Point estimates of the health effects associated with food additives and contaminants can be derived in a number of different units such as, maximum or average individual lifetime or annual excess risk of the health effect, and total expected number of excess cases of the health effect in a given time period. Each of these different measures provides useful inputs for the different risk management decisions associated with protecting the public from foodborne illness. For example, estimated cases can be useful for projecting the population benefits of a particular regulation or compliance monitoring option, while maximum individual risk can help to determine whether the most exposed and susceptible individual will be protected by a certain maximum allowable pesticide residue.

Point estimates can either be derived based on worst case input assumptions or based on the most likely case assumptions. If the output of the risk characterization is to be used for setting maximum permissible exposure levels, then a worst case point estimate may be appropriate. However, if the results are to be used to estimate the benefits of different regulations or compliance monitoring options, then a most likely point estimate is more appropriate.

In both cases, realistic exposure scenarios should be estimated. These include, for each population cohort, estimates of the timing and levels of exposure over their lifetime. In the case of noncarcinogens, both acute and chronic adverse health effects might occur and therefore both short term and long term exposure scenarios should be modeled. For example, the human dose expected to be associated with different levels of salmonella contamination in a single food item can be estimated, under assumptions of typical or worst case food processing activity and portion size. Also, the lifetime human exposure to a heavy metal or carcinogenic pesticide residue can be estimated using estimates of lifetime food consumption (RTI 1984). The results of such an

exposure analysis should be combined with biologically-based models for carcinogenesis or for non-cancer health effects.

An important difference between dose-response modeling for carcinogens and that for non-carcinogens is the greater variety of toxic endpoints to be modeled. For carcinogens a single quantal endpoint, death from cancer, is usually modeled. Carcinogens may also have other adverse effects on humans. However, cancer is assumed to be the critical effect from chronic exposure and is therefore the only one modeled. In the case of noncarcinogens, the identity of the critical effect has not been established so clearly. A single toxic substance may have multiple effects on the same or different target organs. Moreover, since the endpoints are usually not death, the degree to which human health is compromised may vary among the different endpoints, as well as for the same endpoints at different levels of exposure. For example, mercury may have neurotoxic, nephrotoxic, and teratogenic effects. At different levels of exposure to mercury, the neurotoxic effects may not only be more frequently observed in a population but also may be more severe, for example, objective tumors versus appetite loss (MRI 1984). Thus, for noncarcinogens, multidimensional dose-response relationships must be postulated, where the specific exposure scenario (level, duration, dosing frequency etc) is related to both incidence and severity of impact on human health for many different endpoints (Hatch 1972, Hartung and Durkin 1986).

Biologically-based models for carcinogenesis allow for estimation of the impact of different lifetime exposure patterns on the excess annual and lifetime risk of cancer. Examples of such models for cancers are the multistage model and the Moolgavkar-Venzon-Knudson two-stage model (for their use for risk characterization, see Mauskopf and Curtis-Powell 1982, and Mauskopf 1986). Biologically-based models have not yet been developed for noncarcinogens. Such a model would include a threshold below which no harmful health effects will occur. This is because, unlike carcinogenesis, an adverse toxic effect on a single cell is not, in general, sufficient to result in harm to the animal. A certain amount of redundancy exists and cells can be replaced.

Combining a realistic exposure analysis with a biologically-based dose-response model allows for point estimates of the excess health effect risks or cases for given time periods after the start of exposure, as well as estimates of the ages of the victims of such health effects. Using this method, the timing of the

health changes expected after a regulatory change can be estimated explicitly, since the transition from high to lower exposures is modelled explicitly for each population age cohort. Changes in adverse health effects that occur with long latency periods, such as cancer, can be discounted back to the base year if desired. Finally, the possibility of averting behaviors should be taken into account. For example, if the food smells or tastes really bad because of contamination, the purchaser will not consume the product. In this case adverse health effects will be avoided.

2.1 Point Estimates for Carcinogens

The current methods used to derive point estimates in a risk characterization for a population exposed to carcinogenic substances can be summarized by the following relationships:

1. Maximum Individual Risk = $E_{max} \times R$
2. Average Individual Risk = $E_{av} \times R$
3. Total Population Impact = $E_{av} \times R \times N$
4. Annual Population Impact = $(E_{av} \times R \times N) / 70$

where E_{max} = maximum level of exposure
E_{av} = average level of exposure
R = unit risk factor—probability of harmful health effects per unit level of exposure (derived from dose-response relationship)
N = number of people exposed
70 = average life span

The outputs of a cancer risk characterization are typically either measured in units of excess cancer risk or cases of cancer per unit time period.

The exposure estimates have most commonly been based on the assumption of lifetime exposures for an individual at a constant level (USEPA 1987). When more limited exposure durations or changing exposure levels are assumed, weighted average lifetime exposures are estimated (USEPA 1985). Alternatively, cumulative exposures are estimated (Nicholson 1986). Where the parameter values in the exposure assessment are estimated with uncertainty, the point estimates presented are generally those obtained using a worst case exposure scenario (USEPA 1987).

The unit risk factors are estimated using animal or human data. The animal data are typically taken from chronic experiments where the animal has been exposed to a constant level of the carcinogen for most of its lifetime. The human data are taken from natural experiments where the exposure is much more variable and generally is measured as cumulative exposure. In general, linear no-threshold dose-response models are assumed where extrapolation from high experimental or observed doses to lower expected doses is required (USEPA 1987). Furthermore, the upper 95 percent confidence limit value is used for the unit risk factor.

Population size estimates are derived using census data to determine the size of different population cohorts, as well as their geographical distribution. Population cohorts may include divisions according to age, sex, race, smoking habits, or other relevant characteristics.

When estimating the health impact of regulations or compliance monitoring designed to reduce lifetime exposures to carcinogens, the cancer risk estimates with and without the change are compared. The new actions are assumed to change cancer risks because of changes in lifetime exposure levels. In many cases these lifetime exposure levels are estimated assuming an immediate change from the pre- to the post-action exposure level. This does not allow for the fact that some people, for example, may be exposed for 20 years at a higher level before the change, and for the rest of their life at the lower post-action level. Approximately 70 years will be required for this transition period to be completed. In a few instances this transition period is modelled by computing weighted average lifetime exposure levels with and without the change for different age cohorts of the population (USEPA 1985).

Thus, commonly used methods for the generation of point estimates of the excess cancer hazard from exposure to carcinogens use a worst case exposure scenario and weighted average lifetime exposures are computed and combined with unit risk factors estimated using a linearized multistage model. Generally, no account is taken of the different impacts of different lifetime exposure patterns (for example the amounts of different foods eaten may vary with age). No estimates are presented of the timing of the excess cancer cases relative to exposure or of the ages of the victims. And, finally, often no account of the impact on estimated excess cancer cases is taken of the 70 year transition period from high to lower lifetime exposures.

Recently more attention has been paid in the literature to these shortcomings of the point estimates. Crump and Howe (1984) showed the impact of different exposure patterns on estimated excess cancer risk using the multistage model. Various researchers have been exploring the use of the M-V-K model for risk characterization (Murdoch and Krewski 1988, Chen *et al.* 1988, Thorslund 1987, Mauskopf 1986). Other researchers have added a pharmacokinetic component to the multistage or M-V-K models to allow for the possibility of different relationships between applied dose and target organ dose across species or exposure routes (Sielken 1987).

2.2 *Point Estimates for Noncarcinogens*

In general dose-response relationships have not been estimated for noncarcinogenic chemicals or organisms. Instead a threshold dose below which the chemical or organism is assumed to have no adverse effects has been estimated (the reference dose or RfD for chronic exposures, and the threshold limit value or TLV for acute exposures) and used in risk characterization for these chemicals or organisms. Thus risk characterization for a population exposed to a noncarcinogenic substance can be summarized by the following equations:

1. Maximum Individual Risk = 1 if $(E_{max}/(RfD \text{ or } TLV)) > 1$
   = 0 if $(E_{max}/(RfD \text{ or } TLV)) < 1$
2. Average Individual Risk = 1 if $(E_{av}/(RfD \text{ or } TLV)) > 1$
   = 0 if $(E_{av}/(RfD \text{ or } TLV)) < 1$

where

E_{max} = maximum level of exposure for short term or lifetime average
E_{av} = average level of exposure for short term or lifetime average
RfD = reference dose for chronic exposure
TLV = threshold limit value for acute exposure

The ratio of the exposure level to the reference dose gives some indication of the likely severity of the adverse health effects associated with exposure to the toxic substance but, in the absence of a dose-response relationship, quantitative estimates of severity cannot be generated. Using this methodology, popula-

tion effects are best described in terms of the number of people exposed above the reference dose or threshold limit value for either the short or long term and the ratio of their exposure level to the RfD or TLV. Since, both the RfD and the TLV's are estimated with the inclusion of an uncertainty factor, this method gives worst case estimates of the risks at each level of exposure.

More recently, several investigators have estimated dose-response relationships for noncarcinogens and used them for risk characterization. Such dose-response relationships have been estimated for both chronic (USEPA 1985, Crump 1984) and acute (Smith *et al.* 1982, Keeney *et al.* 1982) exposures. Both individual risk estimates and population cases estimates have been generated for a variety of toxic substances. Either single or multiple endpoints have been modeled and, in most cases, relative severity weights have been assigned to the different endpoints. However, since the assumed mathematical structure of the dose-response relationships were not biologically based, such models cannot be used to estimate, for the chronic effects, timing after onset of exposure, or the duration of the effects for affected individuals, or even the impacts of less than lifetime exposures.

2.3 *Unanswered questions*

Although many of the risk characterizations presented in EPA Regulatory Impact Analyses have diverged from the ideal, it is not easy to improve upon them. This is because of our fundamental lack of understanding of the biological mechanisms of action for most substances and health effects. The types of biological questions that remain to be answered for most substances include:

- Is there a threshold dose below which there are no clinically important health effects?
- How can we measure the relationship between the applied dose and the dose at the target organ?
- Is the harmful substance the applied substance or one of its metabolites?
- Is the damage caused by the toxic substance to the cell or organ reversible or irreversible?
- What is the mechanism by which the toxic substance or its metabolite prevents normal cellular function?

To answer these questions for the many potentially toxic substances in the environment an enormous research program would be needed. A program on this scale is not feasible either financially or ethically, because of our inability to perform experiments on humans. In the meantime, closer to ideal point estimates can be obtained by using the data and models currently available and making simplifying assumptions (Mauskopf 1986, Mauskopf and Curtis-Powell 1985).

3. Uncertainty Analysis

There are four sources of uncertainty about point estimates of adverse health effects: uncertainty as to which exposure or dose-response models are correct; uncertainty as to the correct values of the parameters for these models; lack of completeness in the models; and uncertainty due to statistical sampling issues. Uncertainty in the exposure estimates for foodborne carcinogens or noncarcinogens may be due to uncertainty about the level of the toxic substance in the food, or about the relationship between this level and ingested dose or dose at the target organ. Uncertainty in the dose-response estimates may be due to statistical uncertainty from using limited experimental data. When estimating the impact of toxic substances in doses other than the range used in the experiment, more uncertainty is introduced by the choice of the mathematical model for extrapolation from high to low doses. Extrapolation from animal to human exposures introduces yet another source of uncertainty from the computation of equivalent doses and durations.

Ideally all these sources of uncertainty should be assigned individual and joint probability distributions and used to generate, not only most likely or worst case point estimates of the adverse health effects, but also a sensitivity analysis for the point estimates for each input parameter and overall probability distributions for the estimated adverse health effects.

3.1 Uncertainty Analysis for Carcinogens

In general only parameter and statistical uncertainty have been estimated for carcinogens. For these types of uncertainty, several investigators have proposed methods for measuring the uncertainty of the estimated cancer hazards. Midwest Research Institute (1984) proposed a procedure that included estimating ranges for model parameters, sensitivity analysis of selected

factors, and use of propagation of errors for aggregation of uncertainties across a given scenario. A similar approach was used by Tancrede *et al.* (1986). Both of these methods require *a priori* assumptions about the structural relationships between exposure and risk.

Another approach to measuring uncertainty that has been proposed is to choose for each parameter in a model nominal, pessimistic, and optimistic values, then use these values in conjunction with various dose-response models to calculate upper and lower bounds for overall risks (Bogen and Spear 1987). A related approach to measuring uncertainty is to compute several risk estimates from plausible combinations of estimates of the input parameters and estimate the probability of each of these combinations of input parameters occurring. The problem with this approach is assessing the probability of each set of assumptions about the input parameters.

An alternative approach is to estimate probability distributions for each input variable and to use Monte Carlo simulation to estimate the risk distribution (Mauskopf 1985). A problem in this method is that assumptions have to be made about the joint distributions of the various parameters.

Where true uncertainty exists, its magnitude cannot be estimated. Until we have a more complete understanding of the mechanisms of carcinogenesis, such uncertainty will exist about the correct dose-response model. Similarly true uncertainty is present for exposure modelling. The best approach in these cases is to determine which parameters or models are the most important for the cancer risk estimates and to concentrate research efforts on improving our knowledge in that area. Meanwhile, risk characterization should not be considered complete without a quantitative analysis of parameter value and statistical uncertainty for which data are available.

3.2 Uncertainty Analysis for Noncarcinogens

Where point estimates for the risks for noncarcinogens have been derived using the reference dose or threshold limit values, uncertainty analysis has typically not been attempted. An uncertainty factor is included in the estimation of the RfD or TLV, so that, when combined with a worst case exposure scenario, worst case risk estimates are generated, but no attempt has been made to estimate the range of uncertainty for these risk estimates. Such a range could be estimated by combining the results of an uncertainty analysis for exposure, with the uncer-

tainty factors used for computing the RfD or TLV and estimates of the statistical uncertainty of the estimated NOEL.

In the cases where dose-response relationships have been estimated, the same methods as those described above for carcinogens can be used for the uncertainty analysis (MRI 1984).

4. Aggregation of Risks

The parameters used for estimating exposure, unit risk, and exposed population size may vary for a given harmful substance according to the route of exposure and characteristics of the exposed population. If sufficient data are available, disaggregated estimates of average individual risk or population impacts should be generated by route of exposure for different population subgroups. These disaggregated risk estimates should then be aggregated by population subgroup, exposure route, and even across harmful substances taking into account any possible interactions between different substances. Estimates of the range of uncertainty for these aggregate risks should also be generated.

4.1 Aggregating Carcinogenic Risks

The aggregation of risks across population subgroups for a given exposure route and carcinogenic substance is the first step. Estimates of maximum individual risk across population subgroups are not aggregated but compared and the most sensitive subgroup identified. A weighted average individual risk is computed by adding the average individual risks weighted by the relative size of their population subgroup. Finally, total population excess cancer cases are generally estimated by adding the population cancer cases estimates for each subgroup. The problem here is that if conservative exposure and dose-response assumptions have been used to generate the estimates of cancer cases for each population subgroup, the sum of upper bound estimates gives a value for the aggregate risks that are unlikely ever to be experienced. The more appropriate method is to add the mean values of the cancer cases, not the worst case estimates, and combine the variances for each estimate according to standard statistical procedures. An appropriate margin of safety for the sum may then be chosen by the decision maker.

Aggregation of cancer risk estimates across exposure pathways and toxic substances is a more controversial topic. There are

theoretical reasons to believe that, for a single carcinogenic toxic substance, unit risk factors vary according to the route of exposure. This is because these factors are generally computed using the applied dose of the chemical rather than the dose at the target organ. Experience with therapeutic agents also indicates that in many cases the impact of one chemical on the body is changed in the presence of a second chemical, with antagonism being more common that synergism. However, since no data are available for most combinations of carcinogens, it is generally assumed that there is no interaction between these chemicals.

Two different methods for aggregating the risks from carcinogens have been used: dose additivity and response additivity. For dose additivity, the doses (exposure levels) from the different exposure routes or carcinogenic chemicals are weighted by their potencies relative to that of an index exposure route for an index carcinogen, and the sum of all the weighted doses substituted into the dose-response equation for the index carcinogen. For example, for two chemicals or routes of exposure, the excess risk of cancer might be given by:

$$Y = a_1 + b \log(z_1 + pz_2)$$

where

- Y = the excess risk of cancer
- a_1 = the intercept of a log-dose probit response model
- b = the slope if a log-dose probit response model
- z_1 = the dose of the index chemical (or exposure route)
- z_2 = the dose of the second chemical (or exposure route)
- p = the ratio of equitoxic doses of chemicals (or exposure routes) one and two

Application of this method have most commonly assumed a log-dose probit dose-response model, although dose additivity could be applied using any dose-response model including the linear model, $Y = a_1 + b (z_1 + p z_2)$. The equations above can be extended for more than two chemicals (or exposure routes). Dose additivity is the most appropriate method to use for the aggregation of the health risks from multiple exposure routes to a single chemical. The values of the p factors, in this case, will depend on pharmacokinetic parameters for absorption, distribution, and excretion for the different exposure routes. For

aggregation across chemicals, the method of response addition is more commonly used.

In the method of response addition, the excess cancer risks for each chemical are first estimated separately. An assumption is then made as to the correlation of the risks of cancer among carcinogens for a given individual. Most commonly no correlation is assumed. The existence of a genetic predisposition for cancer would indicate that a positive correlation would be more appropriate. However, since the strength of any such correlation is not know it is usually ignored. The formulas for response addition for two carcinogenic chemicals are thus:

$P_3 = P_1$ if $r = 1$ and if $P_1 > P_2$
$P_3 = P_2$ if $r = 1$ and if $P_2 > P_1$
$P_3 = P_1 + P_2 (1 - P_1)$ if $r = 0$
$P_3 = P_1 + P_2$ if $r = -1$ and if $P_3 < 1$

where

P_3 = the total response
P_1 = the response from carcinogenic chemical one
P_2 = the response from carcinogenic chemical two
r = the correlation coefficient

These formulas can be extended to more than two carcinogenic chemicals. With both dose and response addition, as before, use of worst case estimates in the aggregation is undesirable. However, this problem has generally been ignored.

4.2 Aggregation of Noncarcinogenic Risks

Aggregation across exposure routes and toxic substances for noncarcinogens has generally been done in two steps, both of which assume no interaction effects across exposure routes or toxic substances. First, for each toxic response, additivity from different routes of exposure for the same chemical is assumed and a hazard index computed as follows:

Hazard Index, $HI = E_o / Th_o + E_i / Th_i + E_d / Th_d$
where

E_o, E_i, E_d = the exposure levels via ingestion, inhalation, and dermal contact respectively

Th_o, Th_i, Th_d = the RfD's or TLV's for exposure via ingestion, inhalation, and dermal contact respectively

As long as this hazard index has a value of less than 1, exposure to the single constituent chemical is assumed to be without adverse health effects.

If the population is exposed to several chemicals which produce the same toxic endpoint, their hazard indexes are added together. Once again, if this sum is less than one, then the aggregate risk of the maximally or average exposed individual is also assumed to be zero for the particular toxic endpoint. Several aggregate hazard indexes are calculated for all the toxic endpoints for which data are available.

If dose-response functions have been estimated for noncarcinogens then either dose or response additivity can be used for aggregation as for the carcinogens.

5. Concluding Comments

The current less-than-ideal methods for risk characterization for both carcinogens and noncarcinogens have developed largely in response to data limitations and lack of knowledge of the biological mechanism involved that prevent more rigorous approaches. However, more importantly, the current methods were developed for use as inputs to regulations that set safe levels of exposure for the most exposed and susceptible individual. Despite our lack of data, better risk characterization methods might be developed if they are developed with the goal of use as inputs for cost-effectiveness analyses for alternative risk management options.

Risk characterization will approach the ideal when the mechanisms of action of carcinogens and noncarcinogens on the human body are completely understood and when exposure pathways have been accurately modelled. Since this is not likely to happen in the foreseeable future, we cannot expect to be able to achieve the ideal. However, with the knowledge we already have, we can do a lot better than we have been doing. The structure of an ideal risk characterization for use in a cost-effectiveness analysis should be the starting point from which the fewest possible modifications are made to enable us to use the existing data.

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