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Pesticide residues in food: investigation of disparities in cancer risk estimates

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Abstract

Much of the public perceives that exposure to synthetic pesticide residues in the diet is a major cause of cancer. The National Research Council (NRC), in a 1987 report, Regulating Pesticides in Food: The Delaney Paradox, evaluated cancer risks for 29 pesticides that are rodent carcinogens and estimated that the risks for 23 were greater than one-in-a-million. In contrast, our group has ranked possible carcinogenic hazards from a variety of human exposures to rodent carcinogens using the HERP (Human Exposure/Rodent Potency) index, and found that dietary residues of synthetic pesticides ranked low. This paper evaluates the disparities in these analyses by examining the two components of risk assessment: carcinogenic potency in rodents and human exposure. Potency estimates based on rodent bioassay data are shown to be similar whether calculated, as in the NRC report, as the regulatory q_1^* or as TD_{50}. In contrast, estimates of dietary exposure to residues of synthetic pesticides vary enormously, depending on whether they are based on the Theoretical Maximum Residue Contribution (TMRC) calculated by the Environmental Protection Agency vs. the average dietary residues measured by the Food and Drug Administration in the Total Diet Study (TDS). The TMRC is the theoretical maximum human exposure anticipated under the most severe field application conditions, which are far greater than dietary residues measured in the TDS. Several independent exposure studies suggest that the FDA dietary residues are reasonable estimates of average human exposures, whereas TMRC values are large overestimates. Using standard methodology and measured dietary residues in the TDS, the estimate of excess cancer risk from average lifetime exposure to synthetic pesticide residues in the diet appears to be less than one-in-a-million for each of the ten pesticides for which adequate data were available. Published by Elsevier Science Ireland Ltd.

Keywords: Cancer risk; Pesticide residues; Exposure assessment; Carcinogenic potency; Setting priorities

1. Introduction

Possible cancer hazards from pesticide residues in food have been much discussed and hotly debated in the scientific literature, the popular press, the political arena, and the courts [6]. Consumer surveys have shown that much of the US public believes that pesticide residues are a serious cancer hazard [50]. Epidemiologic studies, however, indicate that the major preventable risk factors for cancer are tobacco, dietary imbalances, chronic inflammation from chronic

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infection, and hormones [4]. In the absence of epidemiological data linking pesticide residues to human cancer, the major source of information for assessing potential risks to humans has been the results of high-dose rodent cancer tests. Use of these data requires two types of extrapolation, a quantitative extrapolation from high to low dose and a qualitative extrapolation from rodents to humans.

The purpose of this paper is to investigate the large disparities in published cancer risk estimates for synthetic pesticide residues in the US diet. We examine the extent to which these disparities are due to differences in potency estimation from rodent bioassay data (q_1* vs. TD_{50}) or to differences in estimation of human dietary exposure (Theoretical Maximum Residue Contribution vs. Total Diet Study). The analysis is based on the risk estimates for 29 pesticides, herbicides, and fungicides that was presented by the National Research Council (NRC) in their 1987 report, Regulating Pesticides in Food: The Delaney Paradox [48]. The NRC used potency and exposure estimates of the Environmental Protection Agency (EPA) [19], and concluded that dietary risks for 23 pesticides were greater than one-in-a-million and therefore not negligible. In contrast, we have argued [1,36,38] that risk assessment based on extrapolation of the results of high-dose rodent bioassays to the low doses characteristic of most human environmental exposures should be based on knowledge of the mechanisms of carcinogenesis for each chemical, and that bioassay tumor incidence data are of limited utility in assessing human risk [2,36], in part because about half of all chemicals tested in high-dose rodent bioassays, whether natural or synthetic, are positive and this high frequency may be due to effects of administering high doses. Moreover, quantitatively, potency estimates are bounded by the doses administered in a bioassay [5]. We suggested that in the absence of mechanistic data, the best use of the experimental results was to provide a broad perspective on possible carcinogenic hazards by ranking a variety of human exposures on a simple index, HERP (Human Exposure/Rodent Potency).

The HERP analysis used TD_{50} as a measure of potency [51,53] from animal data and human exposure estimates in order to rank possible carcinogenic hazards from a variety of human exposures to rodent carcinogens including exposures in the workplace, pharmaceutical drugs, indoor and ambient air, naturally-occurring chemicals in the diet, and synthetic pesticide residues. Half the chemicals tested in rodent bioassays are carcinogens, whether naturally-occurring or synthetic, while the vast proportion of human exposures are to natural chemicals. Our results indicate that synthetic pesticide residues in the diet rank low in comparison to many exposures, including the large background of naturally-occurring rodent carcinogens in the diet. The potency and exposure estimates differed between the NRC risk estimates and the HERP ranking, and these differences are examined below to explain the difference in evaluation of possible cancer hazards from synthetic pesticide residues.

The NRC report used the standard regulatory default methodology of the Environmental Protection Agency (EPA) [16,48] to estimate risk, i.e. to evaluate the weight-of-evidence of carcinogenicity for a chemical from chronic rodent bioassays, and extrapolate risk using an upper bound estimate of potency (q_1*) and the linearized multistage model (LMS) [9]. The HERP ranking used the TD_{50} as a measure of potency (the tumorigenic dose-rate for 50% of test animals), and the HERP index is a simple proportion: exposure/potency. In order to compare potency estimates, we first attempted to reproduce the tumor site and incidence data and the q_1* values reported by NRC so that we could use the correct data to estimate TD_{50} and then compare the two estimates. The NRC report did not present the tumor incidence data, and most of these results are not in the general published literature. We obtained the results from EPA memoranda and personal communication, and we present the bioassay data in this paper.

The NRC report and the HERP ranking used two different estimates of human exposure to pesticide residues in the diet. NRC used the EPA TMRC (Theoretical Maximum Residue Contribution) whereas the HERP ranking used the Total Diet Study (TDS) of the US Food and Drug Administration (FDA). The TMRC is a theoretical maximum exposure, whereas exposure in the TDS is measured as dietary residues in table-ready food. We assess the magnitude of the differences between the two potency estimates q_1* and TD_{50} when both use the same rodent results, and then compare the differences between the two exposure

estimates, TMRC and TDS, in order to determine the basis for disparate risk estimates.

Since publication of the NRC report in 1987, the EPA has made several changes in risk estimates of some pesticides in the report. We discuss these changes, including: reevaluations of the weight-of-evidence of carcinogenicity using rodent bioassay results, changes in whether risks should be quantified, changes in exposure estimation, and proposed changes in risk assessment methodology.

2. Methods

2.1. Reproducibility of the EPA q_1* values

The NRC, in Regulating Pesticides in Food: The Delaney Paradox [48], examined the potential human cancer risk for a group of synthetic herbicides, insecticides, and fungicides that EPA had classified as to carcinogenicity based on rodent bioassay data. NRC reported the following EPA data: (1) carcinogenic potency (q_1*); (2) an upper bound estimate of hypothetical, lifetime daily human exposure (TMRC); (3) an upper bound estimate of excess cancer risk over a lifetime, calculated as potency × exposure.

Although the animal results are not presented in the NRC report, we were able to obtain the data from EPA for 19 of the 26 chemicals discussed by NRC [12–15,17,18,20,21,24,28]. We were not able to identify the animal data used in the NRC report for cryomazine, diclofop methyl, ethalfluralin, ethylene thiourea, *o*-phenylphenol, pronamide and terbutryn.

In order to verify that we had correctly identified the rodent results used by EPA in the estimates reported by NRC, we first attempted to replicate the EPA q_1* value for each of the 19 pesticides for which we obtained EPA data. This was required to define the dataset for our comparison of risk estimates. The Tox-Risk program [10] was used to calculate q_1* as the 95% upper confidence limit on the linear term in the LMS, which theoretically represents the slope of the dose-response curve in the low-dose region. If it was not clear which target site had been used by EPA, we calculated more than one q_1* and used in our subsequent comparison of potency estimates whichever data best reproduced the EPA q_1* value. If the EPA memorandum for a chemical stated that the q_1* was the geometric mean of two or more experiments, we used the same method.

The bioassay data that most accurately reproduced the EPA q_1* for each chemical are given in Table 1, along with the EPA weight-of-evidence classification given in the NRC report.

Using the data in Table 1 with the Tox-Risk program, overall there was good reproducibility (Table 2). We were able to reproduce the EPA q_1* value for 15 chemicals within a factor of 2.2, and for 17 within a factor of 6. The median ratio of the q_1* reported by NRC to the recalculated q_1* is 1.1. We could not approximate q_1* for parathion or azinphosmethyl. The q_1* published in the NRC report for azinphosmethyl appears to be an error (pers. comm., W. Burnham, Office of Pesticide Programs, USEPA). We concluded that the dataset of 15 chemicals with q_1* reproducibility within a factor of 2.2 would be used in the comparison of risk estimates. The four chemicals for which we could not reproduce the q_1* within a factor of 2.2 are currently evaluated as not quantifiable for risk estimation by EPA [23], as indicated by the superscripts Cnq and E in Table 1.

2.2. Comparison of potency estimates: q_1* and TD_{50}

Using the incidence data identified as those used by EPA (Table 1), we estimated TD_{50}, which is tumorigenic dose-rate 50, i.e., the dose rate in mg/kg body weight per day that is estimated to reduce by 50% the proportion of tumor-free animals at the end of a standard lifespan [51,53]. TD_{50} does not involve extrapolation to low dose. It is inversely related to slope [51,53], and a comparison with q_1* can be made by using $\ln(2)/TD_{50}$. An adjustment for rodent-to-human extrapolation, such as a surface area or other allometric correction factor, is usually applied to q_1* for regulatory purposes. For comparison purposes, the TD_{50} was adjusted by the same interspecies scaling factor used by EPA for q_1*, i.e. $(\text{bodyweight})^{2/3}$, a factor of approximately 5.5 for rats and 13.0 for mice. The two potency estimates were then compared by computing the ratio $q_1^*/(\ln(2)/TD_{50})$. Some of the experimental results used to calculate TD_{50} in this paper are not reported in the Carcinogenic Potency Database (CPDB) because they are from unpublished EPA studies, whereas the CPDB includes only data from publications in the general literature [39]. The

Table 1

Tumor incidence data used in recalculations of carcinogenic potency for 19 chemicals in the NRC report

Pesticide[a]	Weeks on test	Sex/ species[b]	Target organ	Dose groups (mg/kg per day)[c]	Tumor incidence	TD_{50} (mg/ kg per day)
Acephate[NA(Cnq)]	105	FM	Liver	0,7.5, 37.5, 150	1/62, 3/61, 0/62, 15/61	499
Alachlor [B2]	110	MR	Nasal	0, 0.5, 2.5, 15	0/44, 0/47, 0/44, 15/45	36.8
		FR	turbinate		0/42, 0/42, 1/47, 14/48	
Asulam[NA(Cnq)]	108	MR	Thyroid gland	0, 36, 180, 953	0/43, 9/43, 7/43, (2/40)[d]	724
Azinphosmethyl (Guthion)[D(E)]	114[e]	MR	Thyroid gland	0, 3.9, 7.8	1/9, 10/44, 12/43	31.6
Benomyl[Cq]	104	FM	Liver	0, 75, 225, 1130	1/74, 9/70, 20/75, 15/75	4400
Captafol[B2]	104	FR	Liver	0, 2.8, 12.1, 54.8	4/50, 2/49, 3/50, 17/50	202
		MR	Kidney		1/50, 1/50, 0/50, 7/50	
Captan[B2]	113	FM	Digestive	0, 879, 1480, 2370	3/80, 26/80, 21/80, 29/80	4480
		MM	tract		3/80, 19/80, 22/80, 39/80	
	95	FM		0, 15, 60, 120, 900	0/100, 1/100, 3/100, 4/100, 9/100	
		MM			0/100, 7/100, 1/100, 1/100, 7/100	
Chlordimeform[B2]	104	FM	Hemato-	0, 0.3, 3, 30, 75	3/38, 1/35, 11/42, 31/39, 34/41	21.7
		MM	poietic		3/47, 1/46, 12/46, 32/47, 40/47	
Chlorothalonil[NA(B2)]	129	FR	Kidney	0, 40, 80, 175	0/59, 2/60, 7/57, 19/58	566
Cypermethrin[Cq(Cnq)]	101	FM	Lung	0, 15, 60, 240	12/127, 6/64, 8/64, 14/61	954
Folpet[B2]	113	FM	Digestive	0, 96, 515, 1280	0/104, 1/80, 8/80, 41/80	1910
		MM	tract	0, 93, 502, 1280	1/104, 2/80, 8/80, 41/80	
Fosetyl Al (Aliette)[Cq(Cnq)]	104	MR	Adrenal gland	0, 100, 400, 1510	6/80, 7/78, 16/79, (18/80)[d]	1860
Glyphosate[CqE]	104	MM	Kidney	0, 150, 750, 4500	1/49, 0/49, 1/50, 3/50	62000
Linuron[Cq(Cnq)]	104	MR	Testis	0, 2.5, 6.25, 31.3	4/70, 9/69, 20/70, 37/70	28.1
Metolachlor[Cq(Cnq)]	104	FR	Liver	0, 1.5, 15, 150	0/60, 1/60, 2/60, 7/60	839
Oryzalin[Cq]	104	FR	Skin	0, 15, 45, 135	1/60, 2/60, 4/60, 9/60	394
		MR			5/60, 6/60, 6/60, 24/59	
Oxadiazon[B2(Cq)]	105	FM	Liver	0, 15, 45, 150, 300	4/56, 13/61, 18/64, 27/55, 32/57	213
		MM			20/64, 40/67, 52/69, 44/65, 28/35	
Parathion[Cq(Cnq)]	112	FR	Adrenal	0, 1.15, 2.25	1/10, 6/47, 13/42	7.95
		MR	gland	0, 1.6, 3.15	0/9, 7/49, 11/46	
Permethrin[Cq]	104	FM	Lung	0, 3, 375, 750	15/71, 24/68, 35/68, 44/69	717

[a]EPA weight of evidence evaluation reported as superscript. If two classifications are reported, the values in parentheses are from EPA's revised evaluations since 1987 [24]. B2, sufficient evidence of carcinogenicity from animal studies with inadequate or no epidemiologic data – Probable Human Carcinogen; Cq, limited evidence of carcinogenicity from animal studies in the absence of human data – Possible Human Carcinogen (quantifiable); Cnq: limited evidence (not quantified by EPA); D, human and animal data are either inadequate or absent – Not Classifiable as to Human Carcinogenicity; E, evidence of non-carcinogenicity to humans. NA indicates that the chemical was not classified at the time of the NRC report.

[b]FM, female mouse; MM, male mouse; FR, female rat; MR, male rat. If more than one group is reported, potency calculation is a geometric mean.

[c]Unless mg/kg per day are given in the EPA memorandum, doses are converted from ppm to mg/kg body weight per day by standard EPA conversion factors: 0.05 for rats and 0.15 for mice. All chemicals were administered in the diet.

[d]Doses in parentheses were not used in the calculation of either TD_{50} or the EPA q_1*. For Fosetyl Al the adrenal gland q_1* most closely replicated the NRC q_1*; in later EPA documents urinary bladder was the target site and results were not considered appropriate for quantification [52].

[e]Dosing was only for 80 weeks.

Table 2
Reproducibility of EPA q_1^* values reported by NRC

Pesticide	EPA q_1^* reported by NRC $(mg/kg\ per\ day)^{-1}$	Recalculated q_1^* $(mg/kg\ per\ day)^{-1}$	Recalculated q_1^*/EPA q_1^*
Chlorothalonil	2.4×10^{-2}	1.3×10^{-2}	0.5
Asulam	2.0×10^{-2}	1.4×10^{-2}	0.7
Oryzalin	3.4×10^{-2}	2.5×10^{-2}	0.7
Permethrin	3.0×10^{-2}	2.0×10^{-2}	0.7
Chlordimeform	9.4×10^{-1}	7.2×10^{-1}	0.8
Fosetyl Al	4.3×10^{-3}	3.7×10^{-3}	0.9
Captafol	2.5×10^{-2}	2.4×10^{-2}	1.0
Oxadiazon	1.3×10^{-1}	1.3×10^{-1}	1.0
Cypermethrin	1.9×10^{-2}	2.1×10^{-2}	1.1
Folpet	3.5×10^{-3}	3.8×10^{-3}	1.1
Linuron	3.3×10^{-1}	3.7×10^{-1}	1.1
Captan	2.3×10^{-3}	3.4×10^{-3}	1.5
Alachlor	6.0×10^{-2}	9.5×10^{-2}	1.6
Acephate	6.9×10^{-3}	1.3×10^{-2}	1.9
Benomyl	2.1×10^{-3}	4.6×10^{-3}	2.2
Metolachlor	2.1×10^{-3}	8.7×10^{-3}	4.1
Glyphosate	5.9×10^{-5}	4.8×10^{-4}	6.1
Parathion	1.8×10^{-3}	1.3×10^{0}	720
Azinphosmethyl	1.5×10^{-7}	7.3×10^{-1}	4900000

Recalculated q_1^* uses bioassay data in Table 1 and linearized multistage model.

dose calculation and standardization methods used for TD_{50} calculation in this paper follow EPA methods, some of which differ from the standard methodology to estimate TD_{50} in the CPDB.

2.3. Comparison of human exposure estimates

The risk estimates in the NRC report [48] differed from those in the HERP ranking for dietary residues of synthetic pesticides [1,36,38]. The NRC reported upper bound estimates of daily human exposure, i.e. the EPA TMRC. In contrast, HERP used the daily exposure estimates from the FDA Total Diet Study (TDS). Thirteen pesticides discussed in the NRC report were measured in the TDS, and we compared the exposure estimates from the two sources for these 13. We used results from the TDS for the years 1984–1986 [29,43], which are the closest to the time of the NRC report.

The EPA TMRC is a theoretical maximum estimate for potential human dietary exposure to synthetic pesticides. Pesticides registered for food crop use in the US must first be granted tolerances under the Federal Food, Drug and Cosmetic Act (FFDCA). Tolerances are the maximum, legally allowable residues of the pesticide, or its active ingredient, on raw agricultural commodities and in processed foods [6,48]. A tolerance is typically set for each pesticide for each crop-use (e.g. corn, barley, wheat) based on field trials. The manufacturer conducts these trials, using varying rates of application under diverse environmental conditions, to determine both the minimum application rate needed to be effective against pest targets, and the duration of time before harvest when it has to be applied (these are the rates specified on the pesticide label). Residue measurements are made on various parts of the crop at several time intervals after application, to determine the rate of decline in residues of the pesticide active ingredient, its metabolites, and/or degradation products. The maximum measured residue is then used to establish the tolerance. Each crop-use of a pesticide can have a different tolerance. Thus, the tolerance value is an upper bound estimate of total pesticide residue on a crop in the field, rather than in the marketplace or in table-ready foods.

To obtain the TMRC, the tolerance value is multiplied by the mean US food-consumption estimate for each food item on which the pesticide is legally permitted, and exposures are combined for all such foods. EPA, in calculating TMRC, generally assumes that (1) each pesticide is used on all (100%) acres for each crop that the pesticide is permitted to be used on, and (2) residues are present at the tolerance level (the highest allowable level in the field) in every food for which the pesticide is permitted. The National Food Consumption Survey conducted by the US Department of Agriculture (USDA) is used for average food consumption estimates. Thus, the TMRC represents the hypothetical maximum exposure for a given pesticide, in mg/kg body weight per day, using field trial residue data.

In contrast, the FDA conducts a Total Diet Study (TDS) which measures detectable levels of pesticide residues as they are consumed, using a market basket survey for eight age-sex groups [29–33,35,41,43]. Market baskets of foods are collected four times per year, once from each of four geographic regions of the United States. Each market basket consists of 234 identical foods purchased from local supermarkets in three cities in each geographic area. The foods

are selected to represent the diet of the US population, prepared table-ready, homogenized together and then analyzed for pesticide residues, including some metabolites and impurities [29–33,35,41,43]. The levels of pesticide residues that are found are used in conjunction with the same USDA food consumption data used in TMRC, in order to estimate the average dietary intake of pesticide residues in mg/kg per day [55]. TDS has been conducted annually by FDA since 1961 [31], initiated primarily in response to public concern about radionuclides in foods that might result from atmospheric nuclear testing.

It is important to note that TDS is distinct from FDA regulatory monitoring programs whose primary purpose is to ascertain that residues on crops at the 'farm-gate' or in the marketplace do not exceed maximum allowable levels, and do not result from illegal pesticide use on crops for which the pesticide is not registered. Thus, the FDA regulatory monitoring is designed only to make certain that regulations for pesticide use and application are followed, whereas TDS is designed to provide an estimate of average daily dietary exposure to pesticide residues in foods as consumed. Analytical methods for TDS have been modified over time to permit measurement at concentrations 5–10 times lower than those used in regulatory or incidence level monitoring by FDA. Generally, these methods can detect residues at 1 part per billion (ppb) [29–33,35,41,43].

2.4. Comparison of risk estimates

Of the chemicals for which we were able to reproduce the EPA q_1* reported by NRC, ten were measured in the FDA Total Diet Study, and these were used to compare risk estimates based on different exposure assessments.

3. Results

Our analysis of the sources of variation in cancer risk estimates for dietary synthetic pesticides is presented in Tables 3, 4 and 5. A comparison of the variation in potency estimates to the variation in exposure estimates is given in Table 3. Table 4 reports hypothetical dietary exposure estimates from the NRC report, i.e. TMRC and measured residues in the FDA TDS. In Table 5 risk estimates based on TMRC are compared to risk estimates based on the TDS, using in both cases the EPA q_1* as reported by NRC. Because of missing data or NRC results that could not be reproduced, not all chemicals are included in every table; we have used all chemicals for which appropriate data were available.

We calculated TD_{50} values from the same dose and incidence data in Table 1 that we used to recalculate q_1*, and these TD_{50} values are reported in Table 1. Table 3 compares TD_{50} values to recalculated q_1* values for the 19 chemicals, using the ratio q_1*/(ln (2)/TD_{50}).

The q_1* and TD_{50} values are within a factor of 2 of each other for ten chemicals, and within a factor of 3 for 18 chemicals. Differences in potency values are

Table 3
Comparison of variation in measures of potency and exposure

	Ratio of potency: recalculated q_1*/(ln(2)/TD_{50})	Ratio of exposure: EPA/FDA
Pesticides included in the TDS (FDA)		
Permethrin[Cq]	1.5	579
Acephate[NA(Cnq)]	0.7	1130
Parathion[Cq(Cnq)]	2.6	6300
Azinphosmethyl[D(E)]	6.1	7530
Folpet[B2]	0.8	9650[a]
Linuron[Cq(Cnq)]	2.5	11600
Captan[B2]	1.7	16900
Chlorothalonil[NA(B2)]	1.9	99100
Alachlor[B2]	0.9	–[b]
Captafol[B2]	1.2	–[b]
Cypermethrin[Cq(Cnq)]	2.2	–[b]
Oxadiazon[B2(Cq)]	3.0	–[b]
Pesticides not measured in the TDS (FDA)		
Asulam[NA(Cnq)]	2.5	NA[c]
Benomyl[Cq]	2.2	NA[c]
Chlordimeform[B2]	1.7	NA[c]
Fosetyl Al[Cq(Cnq)]	1.8	NA[c]
Glyphosate[Cq(E)]	2.5	NA[c]
Metolachlor[Cq(Cnq)]	1.8	NA[c]
Oryzalin[Cq]	2.5	NA[c]

[a]Folpet was not detected by FDA in 1984–1986. This value is for 1987.
[b]FDA did not detect any residues, therefore no ratio could be calculated.
[c]Not applicable because not measured by FDA. Asulam had no food uses.

larger only for azinphosmethyl, by a factor of 6.1; there is no statistically significant increase in tumor incidence for azinphosmethyl.

In contrast to the similarity of potency estimation between $\ln(2)/TD_{50}$ and q_1^*, there is enormous variation in dietary exposure estimates for synthetic pesticides between the EPA TMRC values and the FDA average dietary residues in foods prepared as consumed (Tables 3 and 4). For five pesticides (alachlor, captafol, cypermethrin, oxadiazon and pronamide), FDA found no residues at the 1 ppb limit of quantification [29–33,35,41–43,55]. Among chemicals detected by FDA, the TDS estimates were lower than the TMRC estimates by a factor of 99 100 for chlorothalonil, 16 900 for captan, 11 600 for linuron, and 9650 for folpet (Table 3). For four other chemicals, the TDS estimates ranged from 579 to 7530 times lower than TMRC. For the pesticides that EPA classified as having greater evidence of carcinogenicity in animal studies (B2), the differences in exposure estimates for EPA vs. FDA are particularly large. Examination of FDA pesticide residue data collected over a period of 14 years [29–33,35,41,43] indicates that dietary exposure to pesticide residues has not changed markedly over time. Thus, the large differences in exposure estimates between EPA and FDA cannot be explained simply by changes in pesticide use patterns.

In standard regulatory risk assessment, an estimate of the lifetime excess cancer risk is obtained by multiplying q_1^* by human exposure; the true risk, however, may be zero, as the 1986 EPA cancer risk assessment guidelines indicated [16]. A comparison of the risk estimates obtained by multiplying the q_1^* in the NRC report by TMRC vs. TDS exposure values is presented in Table 5. The risks based on TMRC are also reported by NRC, and range from 10^{-3} to 10^{-6}. In contrast, risk estimates using TDS are all lower than 10^{-6}. There are no risk estimates in Table 5 for the chemicals that FDA did not detect, i.e. if there is no exposure, there is no risk. Even if the undetected chemicals are considered to be present in minute quantities, below the limit of quantification, risk estimates for these undetected chemicals would be negligible, i.e. less than 10^{-6}.

Table 4

Dietary exposure estimates of EPA and FDA for pesticides measured in the Total Diet Study[a]

Pesticide	Daily intake (μg/kg per day)	
	EPA TMRC (1986)	FDA TDS (1984–86)
Permethrin^{Cq}	14.0	0.0242
Captan^{B2}	206	0.0122
Folpet^{B2}	92.6	0.0096
Acephate$^{NA(Cnq)}$	5.41	0.0048
Azinphosmethyl$^{D(E)}$	11.3	0.0015
Parathion$^{Cq(Cnq)}$	8.19	0.0013
Linuron$^{Cq(Cnq)}$	4.65	0.0004
Chlorothalonil$^{NA(B2)}$	9.91	0.0001
Alachlor^{B2}	0.408	ND[b]
Captafol^{B2}	23.8	ND[b]
Cypermethrin$^{Cq(Cnq)}$	0.197	ND[b]
Oxadiazon$^{B2(Cq)}$	0.0938	ND[b]
Pronamide$^{Cq(B2)}$	0.486[c]	ND[b]

[a]FDA dietary estimates are for 60–65 year old females, for 1984–1986 [43]. Because of the agricultural usage of these chemicals and the prominence of fruits and vegetables in the diet of older Americans, the residues are slightly higher than for other adult age groups.
[b]Not detected at limit of quantification (~1 ppb).
[c]Did not appear in Tables 1 and 3 because no bioassay data were available.

Table 5

Comparison of cancer risk estimates based on different exposure measures: TMRC vs. TDS[a]

Pesticide[b]	Cancer risk reported by NRC based on TMRC (EPA)	Cancer risk based on TDS (FDA)
Linuron$^{Cq(Cnq)}$	1.5×10^{-3}	1.3×10^{-7}
Captafol^{B2}	5.9×10^{-4}	0
Captan^{B2}	4.7×10^{-4}	2.8×10^{-8}
Permethrin^{Cq}	4.2×10^{-4}	7.3×10^{-7}
Folpet^{B2}	3.2×10^{-4}	3.4×10^{-8}
Chlorothalonil$^{NA(B2)}$	2.4×10^{-4}	2.4×10^{-9}
Acephate$^{NA(Cnq)}$	3.7×10^{-5}	3.3×10^{-8}
Alachlor^{B2}	2.4×10^{-5}	0
Oxadiazon$^{B2(Cq)}$	1.2×10^{-5}	0
Cypermethrin$^{Cq(Cnq)}$	3.7×10^{-6}	0
Each risk	$>1 \times 10^{-6}$	$<1 \times 10^{-6}$

[a]Risk estimates use q_1^* values in the NRC report for pesticides with reproducible q_1^* values (See Table 2, column 1).
[b]Three chemicals measured in the Total Diet Study (Table 4) are excluded: for parathion and azinphosmethyl the q_1^* values could not be reproduced; for pronamide we were unable to obtain bioassay results.

4. Discussion

For synthetic pesticide residues in the diet, large discrepancies in cancer risk estimates are due to differences in exposure estimates rather than to differences in carcinogenic potency values estimated from rodent data. The high risk estimates reported by NRC in 1987 were based on EPA human exposure estimates which assumed that dietary residues were at tolerance levels, which is a large overestimate. For example, the TDS did not detect any residues in table-ready foods for four pesticides that were evaluated in the NRC report as greater than 10^{-6} risks (Table 5).

4.1. Use of rodent bioassays

Carcinogenic potency values, in contrast, were similar for $\ln(2)/TD_{50}$ and q_1^*, and therefore did not contribute substantially to the discrepancies in risk estimation. Similarity in potency estimates is expected: Bernstein et al. [5] showed that carcinogenic potency values from standard bioassays are restricted to an approximately 32-fold range surrounding the maximum dose tested, in the absence of 100% tumor incidence. Estimates of carcinogenic potency derived from statistical models are highly correlated with one another because they are all highly correlated with the MTD [44], regardless of whether the estimate is based on the one-stage, multistage or Weibull model. This constraint on potency estimation contrasts with the enormous extrapolation that is required from the MTD in bioassays to the usual human exposure levels of pesticide residues, often hundreds of thousands of times lower than the MTD.

Standard practice in regulatory risk assessment for chemicals that induce tumors in high-dose rodent bioassays has been to extrapolate risk to low dose in humans by multiplying potency by human exposure. Without data on the mechanism of carcinogenesis, however, the true human risk of cancer at low dose is highly uncertain and could be zero [2,7,8,36,40]. Adequate risk assessment from animal cancer tests requires more information for a chemical, about pharmacokinetics, mechanism of action, cell division, in-duction of defense and repair systems, and species differences. EPA has recently proposed new cancer risk assessment guidelines [26] that emphasize a more flexible approach to risk assessment and call for use of more biological information in the weight-of-evidence evaluation and dose-response assessment. These proposed changes recognize the dose-dependence of many toxicokinetic and metabolic processes, and the importance of understanding cancer mechanisms for a given chemical. The proposed guidelines permit the use of non-linear approaches to low dose extrapolation if warranted by mechanistic data.

Although the proposed guidelines offer some incentive to generate mechanistic data on a chemical, for most chemicals no such data will be available, and the default procedure will continue to be used. The proportion of chemicals tested that are carcinogenic in bioassays is about 50%, whether the chemicals are synthetic or natural, and for a variety of subsets of chemicals tested for carcinogenicity [38]. One plausible explanation for this high positivity rate is that testing at the maximum tolerated dose can cause chronic cell killing and consequent cell division due to cell replacement, a risk factor for mutation and cancer that can be limited to high doses [2,38]. At doses below the toxic effects there might well be no cancer risk, even for rats and mice. Thus, if bioassay data are to be used in risk assessment, it is desirable to facilitate generation of mechanistic data on the chemicals of interest [7], including chemicals for which past risk assessments have resulted in regulation. The EPA guidelines reflect this goal, however, the costs of generating such mechanistic data would have to be added to the already high costs of conducting bioassays. It might be reasonable, therefore for EPA to consider permitting an experimental design that uses (a) a 90-day study to produce mechanistic data to be used in risk assessment, and (b) a reduced protocol for the 2-year bioassay, in order to avoid increasing overall costs. Our earlier anayses indicate that identification of rodent carcinogens, target sites, and strength of evidence can be obtained from a protocol using one sex of each rodent species instead of all four sex-species groups [37,38]. Additionally, the Expert Consensus Panel at a 1992 conference covened by the EPA and the National Toxicology Program was supportive of a reduced protocol [45].

It is noteworthy that in the decade since the NRC report, EPA has reconsidered some of its weight-of-

evidence determinations, and several pesticides are no longer considered appropriate for quantitative risk estimation (see superscripts in parenthesis in Tables). Of the 19 pesticides for which we obtained bioassay data, only 10 are currently considered by EPA as appropriate for quantitive risk estimation (Table 1 superscripts). This contrasts with the NRC report evaluation that the risks for 16 of the 19 were greater than 10^{-6}. For example, linuron had the highest risk estimate of all pesticides analyzed by NRC. It was reclassified as inappropriate for quantitive risk assessment based on biological considerations: the testicular tumors in rats were late-forming and benign and are a relatively common tumor type, the hepatocellular tumors in mice were benign and only in the highest dosed group, and there is no evidence of mutagenic activity [19,24].

Because evaluation of potential carcinogenic hazard to humans is so highly uncertain when the assessment is based on high-dose bioassay data, published risk estimates should include a statement that the true risk at the low doses of human exposure might be zero.

4.2. *Use of exposure assessments*

The results of our analyses emphasize the importance of exposure assessment in risk estimation for synthetic pesticide residues in the diet. Both the TDS of FDA and the TMRC of EPA link estimates of food consumption patterns for groups of individuals with an estimate of pesticide concentrations in food. Since FDA and EPA use the same USDA consumption surveys to estimate dietary patterns, food consumption is not a source of variation in their exposure estimates. However, methods of estimating concentrations of pesticide residues in food differ markedly. FDA measures actual residues in food items that are bought at the market and prepared as typically eaten; EPA uses a theoretical construct, based on worst-case assumptions for the maximally exposed individual and maximally allowable levels, to estimate residues that could legally occur on a given food crop at the 'farm gate' or in the marketplace.

The EPA assumption that every pesticide registered for use on a food commodity is used on every crop is another source of overestimation of exposure [54]. In California, for example, 54 insecticides were registered for use on tomatoes in 1986; however, the maximum number of insecticides used by any tomato grower was 5, 52% of tomato growers used 2 or fewer insecticides, and 31% used none at all [6]. Similar findings are reported for herbicides and fungicides.

FDA monitoring programs have been critcized for not measuring enough pesticides or sampling enough food items, for aggregating foods under a single representative core food (e.g. apple pie to represent all types of fruit pries), and for statistical desgn and sampling. In several other independent studies, however, frequency of detection and residue concentrations have also been consistently low, e.g., residue data from FOODCONTAM, a national data base for state surveys on pesticide and other residues in foods [47]. McCarthy [46] collected residue data on 16 pesticides for 50 crops at the 'farm gate'; although all crops had been treated with the label rates of pesticide application, 93% of 134 samples had concentrations below half the tolerance. Additional treatment of the crops, such as removing husks or outer leaves, shelling, peeling and washing, all reduce residue levels still further [55], as does processing. Eilrich [11] measured residue levels on four produce crops 'from the farm gate to the table' for a fungicide whose active ingredient is chlorothalonil and found that dietary residues were similar to those reported by FDA.

Analyses by Nigg et al. [49] and Winter [54] of residue data from the California Department of Food and Agriculture confirm the FDA regulatory monitoring findings. Most crops have no detectable residues; crop residues that are found are small fractions of tolerance values. Thus, tolerances are poor indicators of human exposure, a function for which they are not designed. Although it is possible that a small percentage of people who obtain food crops close to the farm-gate may have incidental dietary exposures that are above-average, these concentrations are very unlikely to persist over time and would still be substantially lower than TMRC values.

In the TDS, approximately 264 pesticides, metabolites, and impurities are analyzed; only 51 had detectable residues, and only three were present in more than 10% of the sample foods [32]. These findings are similar to those obtained from the TDS during the 10 previous years [29–33,35,41,43], and to those from surveys on pesticides of special interest. Even if

exposure estimates based on TDS were underestimates by an order of magnitude, the potential risks estimated using EPA q_1* would still be low.

The use of TMRC as an estimate of human dietary exposure in quantitative cancer risk assessment is not justified, from either a scientific or public policy perspective, because this measure often grossly exaggerates actual consumer exposure. TMRC uses tolerances as concentration levels in foods, and therefore by definition is not representative of the level likely to reach the consumer [6]. It does not take into account percent of crop treated, actual pesticide application practices, chemical degradation from farm gate to table, cooking or other processing. In recent years many EPA exposure estimates have used 'anticipated residues' instead, which may be calculated using tolerances and processing factors, tolerance and percent of a crop treated, using field trial data, or using monitoring data. The anticipated residue tends to be an overestimate because it is based on the average residue observed from maximum allowable pesticide application of a pesticide during field trials. Actual pesticide use is not always at the maximum level; hence, actual residues tend to be lower than the anticipated level [6]. For example, EPA recently used anticipated residues to evaluate linuron, and reported that less than 1% of the crop of barley, oats and rye was treated. Despite this finding, for risk assessment purposes EPA assumed that 100% of the crop was treated. The linuron comparison indicates how anticipated residues can be an overestimate: the TMRC in the NRC report was 4.65 μg/kg per day; the anticipated residue reported by EPA was 0.185 μg/kg per day [25]; the TDS value was 0.0004 μg/kg per day [43].

4.3. Setting priorities

Current regulatory policy to reduce cancer risk is based on the idea that chemicals that induce tumors in rodent cancer tests are potential human carcinogens; however, the chemicals tested for carcinogenicity in rodents have been primarily synthetic [39]. The enormous background of human exposures to natural chemicals has not been systematically examined. This has led to an imbalance in both data and perception about possible carcinogenic hazards to humans from chemical exposures. The regulatory process does not take into account: (1) that natural chemicals make up the vast bulk of chemicals to which humans are exposed; (2) that the toxicology of synthetic and natural toxins is not fundamentally different; (3) that about half the chemicals tested, whether natural or synthetic, are carcinogens when tested using current experimental protocols; (4) that testing for carcinogenicity at near-toxic doses in rodents does not provide enough information to predict the excess number of human cancers that might occur at low-dose exposures; (5) that testing at the maximum tolerated dose (MTD) frequently can cause chronic cell killing and consequent cell replacement (a risk factor for cancer that can be limited to high doses), and that ignoring this effect in risk assessment greatly exaggerates risks.

The vast proportion of chemicals to which humans are exposed are naturally-occurring. Yet public perceptions tend to identify chemicals as being only synthetic and only synthetic chemicals as being toxic; however, every natural chemical is also toxic at some dose. We estimate that the daily average American exposure to burnt material in the diet is about 2000 mg, and to natural pesticides (the chemicals that plants produce to defend themselves against fungi, insects, and animal predators) about 1500 mg [3]. In comparison, the total daily exposure to all synthetic pesticide residues combined, based on the TDS, is about 0.09 mg [34]. We estimate that humans ingest roughly 5000–10 000 different natural pesticides and their breakdown products [3]. We have shown that a diet free of naturally occurring chemicals that are rodent carcinogens is impossible [38]. It is probable that almost every fruit and vegetable in the supermarket contains natural pesticides that are rodent carcinogens. Even though only a tiny proportion of natural pesticides have been tested for carcinogenicity, 35 of 64 that have been tested are rodent carcinogens and occur in common plant foods and spices. Since 99.9% of the chemicals humans ingest are natural, and the 50% positivity rate for natural chemicals is similar to that for synthetic chemicals, nearly all rodent carcinogens that humans ingest are likely to be natural. Therefore, when risk assessments are published for synthetic pesticide residues, it might help to educate the public and broaden perspective if they were compared to this enormous background of naturally occurring chemicals in the diet.

In the ranking of possible carcinogenic hazards by the HERP index, many naturally occurring chemicals in common foods, including natural pesticides, rank above or close to the median, whereas synthetic pesticide residues rank at or near the bottom. Dietary residues are so low that it seems unlikely that they would be important in human cancer; however, when considering synthetic pesticide residues one wants to identify those that would be priorities of concern. In the HERP analysis, two pesticides rank at the median, which is higher than other synthetic pesticides: 1,1-dimethylhydrazine (UDMH, a breakdown product of Alar) and ethylene thiourea (ETU[2], a common contaminant, metabolite, and degradation product of the group of widely-used ethylenebisdithiocarbamate fungicides [EBDC]).

Strikingly, neither UDMH nor ETU was measured in the TDS. Additionally, positive results in rodent bioassays were published decades ago: in 1973 for UDMH and in 1968 and the early 1970s for ETU. The target sites in those experiments were the same as those used later in regulatory risk assessments from subsequent bioassays. Carcinogenic potency values estimated for UDMH from the 1968 study were similar to those used by EPA for regulation in the late 1980s. For ETU, potency values from positive studies in both rats and mice were in the range of potency values used by EPA in the 1990s for regulatory decisions. What accounts for the fact that these two chemicals were not an earlier focus of regulation, given the enormous regulatory attention given to synthetic pesticides in the diet? Two possible explanations are (1) that inadequate attention has been given to priority-setting and (2) that using TMRC to estimate exposure results in inadequate risk assessment. TMRC distorts the relative importance of the chemicals under consideration because there is wide variation across chemicals in the ratio of the TMRC to the measured exposure, as shown in Table 3: the ratio of exposure for TMRC/TDS ranges from 579 to 99 100, and for four chemicals FDA did not detect any residues. The ratio for ETU using the 1990 market basket estimate is 145, i.e. more similar to TMRC [22,48]. Therefore, risk estimates based on actual exposure would be more similar to those based on TMRC than for the other chemicals. Our analysis has shown that setting priorities is critical, and that regulatory use of the TMRC distorts priorities because there is wide variation across chemicals in the difference between the TMRC and measured estimates of exposure.

[2] ETU was discussed in the NRC report, but we did not receive sufficient information to identify which data were used by EPA for the q_1^* reported by NRC. Some results in our Carcinogenic Potency Database [39] would closely reproduce that q_1^*, and the TD_{50} value would approximate the q_1^*, as it did for the other chemicals in our analysis. The ratio of the TMRC to exposures to the general population in a 1990 market basket study is 145 [22], which is lower than for any of the chemicals in Table 3. Therefore, the 1990 risk estimate for ETU based on measured residues would be more similar to the risk estimate based on TMRC than for other chemicals in our analysis. ETU has had a complex regulatory history, including several q_1^* values, TMRC and market basket exposure estimates, various risk estimates, a cancellation of 11 crop uses of EBDC pesticides in 1992, and a restoration in 1996 of allowable usage for three crops. Since publication of the NRC report, EPA has revised the q_1^* to reflect new bioassay data, then to reflect lower dose data from an in utero study of NTP in mice, and then to reflect a policy change for interspecies extrapolation. The risk estimates have reflected, first, the use of TMRC for exposure, then the 1990 market basket study, and then again to reflect reduced exposures following the cancellation of some uses. The EPA risk estimate based on a q_1^* of 0.11 and the 1990 market basket exposure of 0.0158 μg/kg/day was 1.7×10^{-5} [22]. The 1996 risk estimate based on a q_1^* of 0.06 and exposure after the 1992 cancellation of uses is 0.9×10^{-6} [27].

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