Synthetic Risks, Risk Potency, and Carcinogen Regulation

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Abstract

This article analyzes a comprehensive sample of over 350 chemicals tested for carcinogenicity to assess the determinants of the probability of regulation. Controlling for differences in the risk potency and noncancer risks, synthetic chemicals have a significantly higher probability of regulation overall: this is due to the greater likelihood of U.S. Food and Drug Administration (FDA) regulation. Measures of risk potency increase the probability of regulation by the U.S. Environmental Protection Agency (EPA), have a somewhat weaker positive effect on regulation by the U.S. Occupational Safety and Health Administration (OSHA), and decrease the likelihood of regulation by the FDA. The overall regulatory pattern is one in which the FDA targets synthetic chemicals and chemicals that pose relatively minor cancer risk. The EPA particularly performed more sensibly than many critics have suggested.

INTRODUCTION

Hazardous chemicals are frequent targets of government regulation. In some cases, the presence of significant risks stimulates regulatory action. In other instances, the novelty of newly introduced chemicals or fear of uncertain risks posed by chemicals may contribute to the likelihood of regulation.[1]

Considerable attention has been focused on the role of the synthetic character of the risk influencing the probability of regulation. A series of articles by Ames, Gold, and colleagues has suggested that society regulates many synthetic chemicals that have a lower cancer potency than some of their nonsyn-

[1] Much of this fear of new chemicals stems in part from society's overreaction to new risks that are introduced. This phenomenon is designated the "reference risk" effect by Viscusi, Magat, and Huber [1987] and the "status quo bias" by Samuelson and Zeckhauser [1988]. For a review of risk regulation policy trade-offs more generally, see Morrall [1986].

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thetic counterparts.[2] Their analysis has been largely illustrative in character, indicating an often surprising selection of chemicals for government regulations. Agencies regulate some synthetic risks that are less dangerous than much more potent naturally occurring chemicals.

The inequitable treatment of synthetic chemicals is now emerging as the consensus scientific view. The National Research Council (NRC) [1996] confirms that, for dietary chemicals, "unlike most naturally occurring dietary constituents, synthetic ones such as direct and indirect food additives and pesticide residues are highly regulated, with stringent limits placed on their allowable levels of synthetic chemicals in foods" (p. 303). This result occurs despite the fact that "the committee felt that it is plausible that naturally occurring chemicals present in food pose a greater cancer risk than synthetic chemicals" (p. 309).

Statistical tests by Viscusi [1995], using the selective samples prepared by Gold et al. [1992] to illustrate this phenomenon, indicated a consistent regulatory bias. For these chemicals, there was in fact a synthetic risk bias, controlling for different measures of the magnitude of the risk. The existence of a higher probability of regulation for these synthetic chemicals is not conclusive, however, because the sample used was constructed so as to highlight the apparent overemphasis of government policy in its regulation of synthetic chemicals. This lack of randomness in the sample selection procedure may bias the estimates of the extent of influence of the synthetic character of the risk on the probability of regulation.

To explore these issues without such attendant sampling problems, this article utilizes a comprehensive sample of over 350 chemicals that have been tested for their cancer potency. This risk database is coupled with information on the regulation of these chemicals by the U.S. Food and Drug Administration (FDA), the U.S. Environmental Protection Agency (EPA), and the U.S. Occupational Safety and Health Administration (OSHA). For each of these agencies, and for government regulations more generally, we address a series of fundamental questions pertaining to the character of regulatory policy. First, are synthetic chemicals more likely to be regulated given the level of the risk? Second, what is the influence of the potency of cancer risk on the likelihood of regulation? Third, how do different agencies respond to the attributes of different chemicals in making their regulatory decisions?

The results from this detailed exploration are quite striking and bolster the uneasiness that previous authors and the National Academy of Sciences have expressed with respect to the treatment of synthetic chemicals. The FDA, in particular, is more likely to regulate chemicals if they are synthetic for any given cancer risk level. Moreover, the FDA's regulatory efforts are inversely related to the severity of the cancer risk. Neither the EPA nor OSHA displays a similar synthetic risk bias, and each of these agencies to a differing extent is more likely to regulate more potent carcinogens. These rational targeting aspects of OSHA and EPA efforts are perhaps equally striking, given the criticism their efforts have received.

The next section of the article discusses the legislative constraints and other political factors that may influence regulatory decisions. Then, the article de-

[2] The principal articles that examine the synthetic risk bias and that report on the underlying carcinogenic potency data are the following: Ames [1992]; Ames and Gold [1988]; Ames, Magaw, and Gold [1987]; Ames, Profet, and Gold [1990a]; Ames, Profet, and Gold [1990b]; Gold et al. [1984]; Gold et al. [1986]; Gold et al. [1987]; Gold et al.[1990]; Gold et al. [1992]; and Gold et al. [1993].

scribes the chemical database and presents a characterization of the chemicals in greater detail. These comments are followed by difference-in-means tests and logit regression models which analyze the determinants of the probability of regulation. The final section offers concluding remarks.

THE DETERMINANTS OF GOVERNMENT REGULATION

The Economics of a Conservatism Bias

The economists' usual efficiency prescription for regulatory policy would be to maximize social benefits less costs. These benefits consist primarily of the expected risk reduction, or the probability of the risk multiplied by the exposed population.

In contrast, government agencies do not undertake such benefit–cost balancing but instead focus primarily on the risk component. Moreover, even in the context of this emphasis, there is a focus primarily on the probability of harm to an individual rather than the size of the exposed population. The character of the risk enters as well, as there is a bias against risks that are ambiguous and may turn out to be worse than is initially believed. This form of conservatism bias,[3] which has been inspired in part by a desire to avoid the next thalidomide, contributes to the bias against synthetic chemicals, whose properties may be less precisely known and more novel than those of natural carcinogens.

The desirability of avoiding a conservatism bias is apparent in the following example using the data in Table 1. Suppose that there is 0.5999 chance that there is no risk from a chemical, a 0.4 probability that there is a risk of 0.0002, and 0.0001 probability of a risk level of 0.03. Suppose V is the loss associated with an adverse risk outcome, such as the case of cancer, and C is an index of emphasis placed on the worst-case scenario, which is the chance that the risk could be as high as 0.03. A value of $C > 1$ would indicate a conservatism bias, and $C = 1$ indicates the absence of bias. The expected loss is that given by the data in the third column of Table 1, where the total expected loss is $0.00008V + 0.000003VC$. The bias in effect means that a lower weight V is required to trigger regulation. If preventing a case of cancer is just as important to society whether the risk is big or little, then there is no rationale for a value of C not equal to unity. If there is a desire to be very protective in avoiding risk, one can accomplish this objective by simply selecting a higher value of V to reflect the greater weight society places on preventing cancer.

Some observers have expressed support of conservative risk assessments.[4] One potential economic justification for conservatism bias in treatment of synthetics could be that government regulations will affect incentives for innovation. These incentives are more consequential for new synthetic chemicals than for natural chemicals. If the risk a chemical poses is exogenous, which is likely in the case of nonsynthetics, the regulator simply sets the threshold with respect to efficient social risk tolerance. But synthetic risks may be endogenous in that the choice of a regulatory threshold also will influence the choice of

[3] For advocacy of such an approach, see Krier [1990], and for a critique see Nichols and Zeckhauser [1986], Viscusi [1992], and Paté-Cornell [1996, pp. 13–14].

[4] Krier [1990], for example, takes a more positive view.

Table 1. Example to illustrate conservation bias.

Probability of risk level	Risk level	Expected loss
0.5999	0.0000	0.000000
0.4000	0.0002	0.00008*V*
0.0001	0.0300	0.000003*VC*
	Total	0.00008*V* + 0.000003*VC*

investment in safety by those designing synthetics. Whether regulators might want to set different standards for synthetic chemicals because of this incentive effect is a matter beyond the scope of this article.

Legislative Influences

Before 1976, most legislation dealt with health risks only, usually explicitly mandating the reduction of risk to zero or threshold levels.[5] Over time, our technological capabilities for identifying trace amounts of hazardous substances increased [Menzer and Nelson, 1980, p. 838; Van Middelem, 1971, p. 315]. At the same time that people were first learning of the presence of additional chemicals in foods, water, and air, advances in toxicology as well as increased numbers of epidemiological studies and bioassays resulted in rapid increases in the number of substances suspected of being carcinogenic. Moreover, as the risks were newly recognized, it was initially thought that the newer substances were largely to blame, and synthetics received undue attention, as there is a tendency to overestimate novel risks, particularly those with low probabilities [Viscusi, 1992, pp. 101–108].

Over time, scientists began to place less importance on the dangers of synthetic chemicals. For example, Sir Richard Doll and Richard Peto [1981] estimated that, even though nearly one third of cancers were caused by diet, only 1 percent of these cancers were due to chemical additives in food (including pesticides). As scientists have gained experience conducting risk analyses and regulators have gained more experience interpreting the findings, standards set under newer programs consequently may have been more trusting of risk quantification methods, and thus more reflective of quantitative risk than older programs.[6] Moreover, newer standards may demonstrate less of the initial misperception that synthetics are the predominant source of risk.

As the following legislative review will indicate, differences in the timing of the legislative mandates may have affected their character. The legislative constraints on the EPA and OSHA are broad. The laws require the agencies to reduce risk but do not define the mission narrowly. In contrast, much of the FDA's approach to toxic substances was derived from the Delaney Clause, a set of three amendments made to the Federal Food, Drug, and Cosmetic Act between 1958 and 1961.

[5] For a historical review, see Zimmerman [1990, pp. 38–43].

[6] Agency discretion is a much debated topic in political science and public policy circles. For discussion of agency discretion and congressional control theories, see McNollgast [1989], Asimow [1994], and Hamilton and Schroeder [1994].

The Food and Drug Administration

Regulation of chemical substances under the Federal Food, Drug, and Cosmetic Act differs according to the intended use of the substance. Applications for use of proposed new pharmaceuticals will be rejected if they fail to show safety and efficacy. Food additives face a similar licensing scheme whereby the Secretary of Health and Human Services promulgates a regulation for an additive's use upon demonstration that the additive is safe within its intended use. This demonstration requires extensive prepetition toxicological testing on the part of the additive's proponents [Stever, 1986, p. 8–7].

The statutory definition of a food additive is "any substance the intended use of which results or may reasonably be expected to result in its becoming a component of or otherwise affecting the characteristics of any food . . . if such substance is not generally recognized . . . to be safe under the conditions of its intended use" [21 U.S.C. § 321(s)]. This definition excludes color additives, substances used under sanctions issued prior to 1958, pesticides, and new animal drugs [Merrill, 1988].

Color additives face a licensing scheme nearly identical to that for food additives. Other noncarcinogenic "added substances" (that is, those which do not fit the definition of "food additives") will not be deemed adulterated unless there is a showing by the government that the substance "may render" foods "injurious to health" [21 U.S.C. § 321(a)(1)]. The Delaney Clause is the most important FDA regulation for synthetic chemicals as it regulates food additives, color additives, and animal drug residues. That regulation states that "no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man and animal . . ."[7] The result of this unique zero-risk rule is that the regulation of food additives relies almost entirely upon finding the substance to be carcinogenic and is unrelated to the quantified toxicity value.

Two biases will result as a joint consequence of the FDA licensing scheme and the Delaney Clause. First, there will be relatively fewer natural substances being regulated than would be the case if the FDA searched for and regulated risk, as do OSHA and the EPA. As the Delaney Clause applies only to food additives, additives are regulated more heavily than nonadditives. The group of substances considered food additives is primarily synthetic, as most natural substances which occur in processed foods are either food products or are the results of decomposition or cooking of food.

The second bias stems from the costs of the FDA licensing scheme. Firms will not petition for approvals unless there is a reasonable probability of the petition's success.[8] The result of this self-selection is that firms will not submit truly highly toxic substances for approval unless there is a compelling reason for granting approval or a substantial payoff if the petition is approved. To

[7] 21 U.S.C. § 348(c)(3)(A) for food additives. The language for color additives is identical. See 21 U.S.C. § 321 (c)(3)(A).

[8] The directions for contents of a petition for intended use of a food additive, for example, are listed in 21 U.S.C. § 348(b)(2). Submissions must include information on the identity of the substance, detailed statements of the conditions for proposed use, data on the effects and side effects resulting from use, methods for testing, and results of testing for health effects. The compilation of this information is far from costless.

further the bias, the effort spent in running the licensing program takes resources away from searching for substances which "may render" food "injurious to health." [9] This reduces the emphasis likely to be placed on dangerous natural chemicals.

One attempt by the FDA to reduce the number of food additive applications is to consider substances which were approved prior to 1958 as being "Generally Regarded as Safe" (GRAS) to be used as food additives. A substance can also be added to this category if it is "generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures . . . to be safe under the conditions of its intended use [21 U.S.C. § 321(s)]. That requirement is considered met if there is "reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use [41 Fed. Reg. 14483 (1977)]. The existence of these lists dampens the influence of the self-selection bias, as it has prevented dozens of substances from having to reapply for certification as food additives.

Occupational Safety and Health Regulation

The Occupational Safety and Health Act provides that standards established by OSHA are to "assure so far as possible every working man and woman in the Nation safe and healthful working conditions. . . ."[10] More specifically:

> [T]he Secretary, in promulgating standards dealing with toxic materials or harmful physical agents under this subsection, shall set the standard which most adequately assures, to the extent feasible, on the basis of the best available evidence, that *no employee* will suffer material impairment of health or functional capacity *even if such employee has regular exposure to the hazard* dealt with by such standard *for the period of his working life.* (29 U.S.C. § 655 (b)(5)); emphasis added

This legislative language and subsequent court rulings make it clear that the basis of both the establishment and stringency of OSHA standards is to reduce the risk faced by the individual worker to *de minimis* levels whenever feasible.[11] This mandate calls for regulation of all (and only those) substances which are more toxic than some threshold value for which control is feasible. Because the agency also has substantial discretion as to which risks are to be given regulatory priority, we should expect that the probability of OSHA regulating a given substance will be directly related to that substance's toxicity and will be uncorrelated with the synthetic/natural character of the substance (provided that one is controlling for toxicity, or that toxicity is unrelated to the character of a substance).[12]

This concern with risk levels rather than the source of the risk is also reflected in the preamble of the 1989 Permissible Exposure Limit (PEL) revisions, which

[9] 21 U.S.C. § 342(a)(1). Currently these bans apply to only eight substances in our data set: benzene, chloroform, 4,4′-methylenebis (2-chloroaniline), nicotine, safrole, sodium cyclamate, thiourea, and toluene).

[10] 29 U.S.C. § 651(b). (Also Pub. L. 91-596, § 6(b) (1973)).

[11] See *ATMI v. Donovan* [1981]; *Industrial Union Dept. v. American Petroleum Institute* [1980]; *AFL-CIO v. OSHA* [1992].

[12] *United Steelworkers v. Auchter* [1985] allows the agency to "set priorities for the use of the agency's resources and to promulgate standards sequentially."

includes several statements to justify selection of substance groups on grounds of maximizing the health benefits of the revisions and for reducing rulemaking costs in an efficient manner [54 Fed. Reg. 2363, 2373]. Synthetic chemicals receive no special prominence.

The Environmental Protection Agency

Unlike OSHA, the EPA was not formed by a legislative act, but rather through an administrative reorganization.[13] As a result, its legislative text is quite diverse. The vast majority of the substances regulated by the EPA are regulated through the Clean Air Act (CAA); the Clean Water Act (CWA); the Toxic Substances Control Act (TSCA); the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA); the Safe Drinking Water Act (SDWA); the Resource Conservation and Recovery Act (RCRA); and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). These acts, as categorized by Zimmerman [1990], typically couch the criteria for regulation to be "significant" or "substantial" risk (pp. 60–64). This approach is more consistent with a population risk objective than that for the OSHA standards, which are labeled as "zero risk" or "threshold risk." The exception to this generalization is the SDWA, which also uses threshold risk for Maximum Contamination Limits (MCLs) and zero risk for some MCL goals.

As an example of EPA management guidelines, the Clean Air Act (CAA), as most recently amended in 1990, establishes national primary ambient air quality standards, which, "allowing an adequate margin of safety, are requisite to protect the public health" [42 U.S.C. § 7409 (b)(1)(1990)]. This phrasing can be interpreted as far less restrictive than that for OSHA chemical standards, as it would allow risk to individuals so long as the overall threat to the population posed by the substance was insubstantial. But for "public health" regulations, as for individual risk standards, the probability of regulation will increase as the toxicity of the substance of concern increases, other things equal. Moreover, there is no reason to expect a bias against synthetics in any of the individual pieces of EPA or OSHA legislation, and this trend should be borne out when looking at the agencies' regulatory patterns as a whole.

CHEMICAL CHARACTERISTICS AND REGULATORY POLICY: MEAN EFFECTS

The database used for this analysis draws upon the 1993 version of the Carcinogenic Potency Database (CPDB) developed by Ames, Gold, and collaborators.[14] The sample will consist of all 365 chemicals for which there is carcinogenicity information for both male and female rats and for which potential chemical exposures could be indentified in the *Encyclopedia of Chemical Technology.* Thus, this sample will not be limited to the 51 dietary rodent carcinogens that were used for illustrative purposes in previous research.[15] For those selected samples, the emphasis was on comparing many regulated carcinogens with well-known carcinogenic exposures, such as the presence of caffeic acid

[13] The National Environmental Protection Act of 1970 (NEPA) (42 U.S.C. § 4331 et seq.) established the National Council on Environmental Quality, which formed a basis for the EPA, but NEPA did not include risk management guidelines in its text.

[14] More specifically, we use Gold et al. [1993].

[15] These more selective samples are discussed in Ames, Profet, and Gold [1990b], Gold et al. [1992], and Viscusi [1995].

in lettuce, apples, pears, coffee, plums, celery, carrots, and potatoes. Those articles demonstrated that many natural carcinogens in the human diet pose higher cancer risks than regulated synthetic chemicals.

Statistical analysis of that smaller database by Viscusi [1995] demonstrated that there was a significant relationship between the synthetic character of the risk and the probability of government regulation. This relationship held for a variety of measures of risk magnitude. The risk levels themselves, however, appeared to be inconsequential to the probability of regulation.

Although these formal tests are instructive, they are not conclusive because of the limited nature of the sample. In this article, we seek to determine whether the synthetic character of the risk influences regulatory decisions. In addition, we will be asking a second question that was not discussed in the Ames, Profet, and Gold [1990b] and the Gold et al. [1992] inquiries, which is whether risk potency matters at all in determining regulatory decisions.

The Carcinogenic Potency Database (CPDB) was most recently updated in 1993. That source, updated occasionally in *Environmental Health Perspectives,* lists over 1200 substances [Gold et al., 1984; Gold et al., 1986; Gold et al., 1987; Gold et al., 1990; Gold et al., 1993]. This number includes substances which have only been tested in one species, or which were tested for only one gender in that species, or which gave inconclusive bioassay results. We limited the sample to those substances which had been tested on rats in order to eliminate interspecies variation and reduce questions on how to quantify substance toxicity given multiple testing results. The number of substances tested upon each species was roughly equal, and the rat tests translate more easily to human weight equivalents.[16]

Among those substances tested in rats and for which human exposure pathways could be determined from the *Encyclopedia of Chemical Technology,* there was complete carcinogenic toxicity information for 365 substances. For these purposes, complete toxicity information means that the substance tested to have negative results in both male and female rats, or that there was a positive result quantifiable as a TD_{50} value. A TD_{50} value is the quantity of the chemical substance, measured in milligrams of substance per kilogram of animal body weight per day, which when administered chronically, causes half of the animals to develop tumors over the course of a lifetime. This value will be used to represent a substance's carcinogenic potency.

Low TD_{50} values indicate a very potent chemical that causes tumors in very small doses, whereas high TD_{50} values indicate a weaker carcinogen. We designate chemicals for which there was no carcinogenic dose level observed (that is, there is no TD_{50} value found) by the variable *NOT CARCINOGENIC* = 1. Chemicals for which a low level of exposure causes tumor formation (those substances with a TD_{50} value smaller than the median, provided the substance is tumorigenic) will be captured using an indicator variable, *HIGH TOXICITY* = 1.

Although TD_{50} values serve as a general benchmark for riskiness because they are strongly correlated with other measures of toxic effects such as the maxi-

[16] Viscusi [1995] reports findings for both rat and mice TD_{50} values. That analysis was also undertaken using Human Exposure/Rodent Potency (HERP) values from the Ames, Profet, and Gold [1990b] and the Gold et al. [1992] studies and carcinogenic slope factors from the EPA's Integrated Risk Information System (IRIS) database. In each case, the results reported are similar to those obtained using the rat TD_{50} and mice TD_{50} values.

mum tolerated dose (MTD), cancer risk is not the only hazard derived from chemical substances.[17] Chemicals may contribute to kidney, liver, lung, or heart diseases, or a wide variety of other noncarcinogenic ailments. In order to control for these risks, each substance in the sample was cross-referenced to the EPA's Integrated Risk Information System (IRIS), which contains noncarcinogenic toxicity information for hundreds of substances in the form of reference doses. The reference dose (RfD) is the maximum amount of the substance, which, if administered chronically, is unlikely to have a significant adverse effect upon the person exposed. When known, this dose was entered into the database in units of milligrams of substance per kilogram of animal body weight per day (mg/kg·day).

Unfortunately, the EPA has identified reference dose levels for only 75 of the 399 substances in the sample. Some substances without RfD values are safe, and others have risks that have not yet been identified. We designate missing reference dose values using an indicator variable named *NO REFERENCE DOSE* = 1 if missing, 0 if not.

To classify chemicals regarding their synthetic or natural character, we used information from the *Dictionary of Natural Products* (DNP), which contains an exhaustive list of thousands of natural substances and the *Merck Index*. We classified substances not indicated as natural products in the *Merck Index* and absent from the DNP as synthetic. We identified different substances using the unique Chemical Abstracts Service (CAS) numbers listed in the CPDB, and thus eliminating the chance of missing a substance entry through ignorance of that substance's synonyms.

We drew information on the regulation of substances from the *Code of Federal Regulations* (CFR), 1994 edition. Using CAS numbers for identification where possible, and all known synonyms when CAS numbers were not used in the CFR, we constructed indicator variables to record whether the substance was regulated by the EPA, the FDA, OSHA, or the Department of Transportation, or if the substance was declared to be GRAS by the FDA.

Table 2 summarizes the profile of the chemicals for which there is some evidence of carcinogenicity. Overall, 184 of the chemicals, or 51 percent, did not have any evidence of carcinogenicity based on the rat bioassays. Differences based on whether there is evidence of carcinogenicity appear in the final column of the table, where superscripts indicate pertinent levels of statistical significance based on *t*-tests of the difference in means for the two columns. The synthetic character of the risk is not significantly related to evidence of carcinogenicity.

Tumorigenic substances are less likely to have an RfD in the IRIS database, perhaps because the existence of one toxicity value reduces uncertainty enough to warrant spending research dollars elsewhere. Substances that are not carcinogenic have a higher reference dose level than carcinogenic substances, reflecting the greater amount of chemical exposure that is permitted before these noncarcinogenic substances become risky in other ways. This indicates a multidimensional aspect to chemical risk, as also found by the NRC [1996].[18]

[17] The National Research Council (NRC) [1996] reports, for example, that several investigators have noted a strong correlation between the TD_{50} and the MTD (p. 260), and also relates findings from studies by Travis et al. [1990], Travis, Saulsbury, and Pack [1990], and Travis, Wang, and Wachner [1991] that there is a strong correlation between TD_{50} and a composite potency index drawn from the Registry of Toxic Effects of Chemical Substances (RTECS) data (p. 263).

[18] See footnote 17.

Table 2. Means conditional upon carcinogenicity of the substances.

Variable	NOT CARCINOGENIC = 1 (N = 184)	NOT CARCINOGENIC = 0 (N = 181)	Difference
SYNTHETIC	0.723	0.740	0.017
	(0.449)	(0.440)	
NO REFERENCE DOSE	0.761	0.862	0.101[b]
	(0.428)	(0.346)	
REFERENCE DOSE LEVEL (RFD)	0.911	0.136	−0.775
(N=44, 25)	(4.559)	(0.395)	
REGULATION	0.587	0.669	0.082[a]
	(0.494)	(0.472)	
FDA REGULATION	0.449	0.372	−0.077
(N=107, 86)	(0.500)	(0.486)	
EPA REGULATION	0.435	0.586	0.151[c]
	(0.497)	(0.494)	
OSHA REGULATION	0.169	0.282	0.113[c]
	(0.375)	(0.451)	

Notes: Standard deviations are in parentheses; t-test are two-tailed.
[a]t-statistic = 1.61.
[b]Significance level = 0.05.
[c]Significance level = 0.01.

The next sets of variables pertain to overall government regulation and regulation by the FDA, the EPA, and OSHA. The expected direction of influence is that if the rats do not develop tumors then government regulation should be less likely. This relationship is borne out in the case of the EPA and OSHA, where the differences are statistically significant at the 1-percent level. Somewhat surprisingly, FDA regulations are more likely to exist for chemicals not found to be carcinogenic, which is the opposite of what one would expect. Subsequent regression results will analyze the determinants of regulation by each of these agencies, controlling for the different influences at work.

Table 3 indicates how the synthetic character of the risk is related to measures of the risk level as well as the frequency of regulation. There is no evidence that the 267 synthetic chemicals are more dangerous than the 98 nonsynthetic chemicals in the data set. There are no statistically significant differences between synthetic and nonsynthetic chemicals for any of the three cancer risk measures listed or for the noncancer risk measure. Indeed, the point estimates of their values reflect somewhat safer levels for the synthetic chemicals. Synthetic chemicals have a higher reference dose level, indicating that more exposure is needed to generate noncancer health effects. The TD_{50} value for synthetic chemicals in rats is also somewhat higher—indicating lower average carcinogenic potency, although the differences are not statistically significant.[19]

Although the synthetic character of the chemical is not a significant determinant of the risk level based on these partial tests, the synthetic character is significantly linked to the probability of regulation. The two statistically significant differences between synthetic and nonsynthetic risks in Table 3 are

[19] Means for RfDs and TD_{50} values are conditional upon the existence of quantified values for that variable, in order to prevent biases caused by assigning weight to missing values. The numbers of observations on which these statistics are based are in parentheses.

Table 3. Means conditional upon the synthetic character of the substances.

Variable	SYNTHETIC = 1 (N = 267)	SYNTHETIC = 0 (N = 98)	Difference
NOT CARCINOGENIC	0.498	0.520	0.022
	(0.501)	(0.502)	
RATS TD_{50}	321.3	302.4	−18.9
(N = 134, 47)	(842.9)	(1325.5)	
HIGH TOXICITY	0.240	0.265	0.025
	(0.428)	(0.444)	
NO REFERENCE DOSE LEVEL	0.790	0.867	0.077[a]
	(0.408)	(0.341)	
REFERENCE DOSE LEVEL (RFD)	0.706	0.304	−0.402
(N = 56, 13)	(4.049)	(0.552)	
REGULATION	0.640	0.592	−0.048
	(0.481)	(0.494)	
FDA REGULATION	0.473	0.337	−0.136[a]
(N = 110, 83	(0.502)	(0.476)	
EPA REGULATION	0.524	0.469	−0.055
	(0.500)	(0.502)	
OSHA REGULATION	0.213	0.255	0.042
	(0.411)	(0.438)	

Notes: Standard deviations are in parentheses; t-tests are two-tailed.
[a]Significance level = 0.10.
[b]Significance level = 0.05.

that synthetic risks have a 0.05 higher probability of regulation by government agencies overall and a 0.14 higher probability of regulation by the FDA. The synthetic character of the risk has a minor and not statistically significant influence on the likelihood of regulation by either the EPA or OSHA.

These results do not, however, control for the magnitude of the risk and its influence on regulatory behavior. However, as the subsequent regression results will indicate, these findings are not only suggestive of the directions of influence but also the overall magnitudes of the effects at work.

ECONOMETRIC TESTS

Consider first the issue of whether a chemical is regulated by any of the three government agencies listed—the FDA, the EPA, or OSHA—Table 4, (panel A) provides a summary of the differences between the 229 chemicals that are regulated and the 136 that are not. In terms of mean differences based on this characteristic, there are three significant differences between the two columns. Regulated chemicals are 12 percentage points more likely to be highly toxic and have a probability 0.27 higher of exhibiting noncarcinogenic toxicity.

These same relationships also are borne out after controlling for each set of influences at work. Table 4 (panel B) presents the logit regression results for the determinants of the probability of regulation. Each equation includes variables characterizing the synthetic character of the risk and whether there was evidence of carcinogenicity. Two different measures of the magnitude of the risk are also included. The second equation includes the high toxicity variable to capture the influence of particularly risky chemicals; that is, chemicals for

Table 4. Overall federal government regulation.

Panel A. Variable means conditional upon whether the substance is regulated.

Variable	Regulated (N = 229)	Unregulated (N = 136)
SYNTHETIC	0.747	0.706
	(0.436)	(0.457)
NOT CARCINOGENIC	0.472	0.559
	(0.500)	(0.498)
RATS TD_{50}	345.3	258.1
(N = 121, 60)	(1141.2)	(567.2)
HIGH TOXICITY	0.293[c]	0.169[c]
	(0.456)	(0.376)
NO REFERENCE DOSE	0.712[c]	0.978[c]
	(0.454)	(0.147)
REFERENCE DOSE	0.657	0.044
(N = 66, 3)	(3.734)	(0.050)

Panel B. Logit regression results for probability REGULATION = 1

Variable	Coefficient (asymptotic standard error) Model 1	Model 2
INTERCEPT	3.265[c]	2.896[c]
	(0.705)	(0.721)
SYNTHETIC	0.043	0.066
	(0.258)	(0.261)
NOT CARCINOGENIC	−1.486	−0.189
	(1.729)	(0.281)
RATS TD_{50}	9.2×10^{-5}	—
	(1.8×10^{-4})	
HIGH TOXICITY	—	0.837[b]
		(0.335)
NO REFERENCE DOSE	−4.092	−4.186
	(3.145)	(3.231)
REFERENCE DOSE	1.996	2.102
	(5.275)	(5.426)

Panel C. Effect of change in variable from 0 to 1

Variable	Model 1	Model 2
SYNTHETIC	0.01	0.01
NOT CARCINOGENIC	−0.30	−0.04
HIGH TOXICITY	—	0.17
NO REFERENCE DOSE	−0.83	−0.84

Panel D. Effect of change in variable from 0 to mean value.

Variable	Model 1	Model 2
RATS TD_{50}	0.01	—
REFERENCE DOSE	0.26	0.27

Note: Standard deviations for means and asymptotic standard errors for parameter estimates are in parentheses; t-tests are two-tailed.

[a]Significance level = 0.10.
[b]Significance level = 0.05.
[c]Significance level = 0.01.

which the TD_{50} value was below the median TD_{50} value, or 30.5 mg/kg·day.[20] The first equation includes the rats' TD_{50} value, which is a continuous measure of the degree of riskiness. There is one substantive variable that is statistically significant at the 5-percent level (two-tailed test). The synthetic risk variable does not have a significant effect. However, the high-toxicity variable exerts a positive influence which is consistent with sound risk-reducing regulatory policies.

The extent of the influences implied by the regression estimates appears in Table 4 (panel C). Changing the value of the synthetic risk variable from 0 to 1 increases the probability of regulation by 0.01 in each, but these effects are not statistically significant.

Variables that are highly toxic based on the TD_{50} value similarly have a higher probability of regulation of 0.17. Because the rats' TD_{50} value is a continuous variable, to characterize its influence Table 4 (panel C) calculates the effect of a change in the value of that variable from 0 to its mean amount. The mean effect of this variable on the probability of regulation is 0.01, so that the magnitude of the influence is small, as is its statistical significance.

FDA Regulation

Table 4 focuses on the entire sample of 365 chemicals for all regulatory agencies. Differences across agencies in regulatory actions will tend to blur the underlying agency policies. Table 5 assesses the determinants of the probability of regulation by the FDA of the 193 tested chemicals that are present in foods, drugs, or cosmetic products. Overall, just over two fifths of these chemicals are regulated by the FDA. In terms of the mean effects shown in Table 5 (panel A), the most striking influence of interest is that regulated chemicals are 14 percentage points more likely to be synthetic, an effect which is significant at the 10-percent level. The risk variables have an influence that runs counter to one's expectations. Regulated chemicals are 8 percentage points more likely to be noncarcinogenic. A more statistically significant influence is whether the chemical is highly toxic, which reduces the likelihood of regulation. Even the rats' TD_{50} value—a variable inversely related to riskiness—is 122 percent higher for the regulated substances. A higher TD_{50} value indicates a higher dose level before the substance is found to be carcinogenic. Regulated chemicals also are more likely to have a higher reference dose level. These simple breakdowns suggest that the FDA is less likely to regulate substances that are risky and much more likely to regulate synthetic chemicals.

Table 5 (panel B) presents the logit regression results in order to control for the partial influences of the key variables. The synthetic character of the risk remains a strong contributor to the probability of regulation. Based on the estimates in panel C, a synthetic chemical has a probability of 0.12 to 0.13 higher of being regulated, controlling for various measures of the risk level. In the second equation including the high-toxicity variable, the *NOT CARCINOGENIC* variable is not significant, but highly toxic chemicals have a significant

[20] Examination of the relationship of the probability of government regulation to the TD_{50} value suggested that this relationship was nonlinear. Inclusion of the natural logarithm or a quadratic TD_{50} value term in the regression analysis did not capture the extent of the influence and, as a result, the alternative that was selected was to use an indicator variable for TD_{50} values below a particular high-risk threshold.

Table 5. Food and Drug Administration (FDA) Regulation.

Panel A. Variable means conditional upon whether the substance is regulated by the FDA.

Variable	FDA Regulation = 1 (N = 80)	FDA Regulation = 0 (N = 113)
SYNTHETIC	0.650[a]	0.513[a]
	(0.480)	(0.502)
NOT CARCINOGENIC	0.600	0.522
	(0.493)	(0.502)
RATS TD_{50}	599.1	269.7
(N = 32, 54)	(1427.3)	(1241.1)
HIGH TOXICITY	0.138[b]	0.283[b]
	(0.347)	(0.453)
NO REFERENCE DOSE	0.788[c]	0.938[c]
	(0.412)	(0.242)
REFERENCE DOSE	0.190	0.013
(N = 17, 7)	(0.489)	(0.011)

Panel B. Logit regression results for probability FDA REGULATION = 1

	Coefficient (asymptotic standard error)	
Variable	Model 1	Model 2
INTERCEPT	−0.443	(0.136)
	(0.640)	(0.686)
SYNTHETIC	0.581[a]	0.549[a]
	(0.316)	(0.318)
NOT CARCINOGENIC	−1.597	−0.052
	(0.711)	(0.379)
RATS TD_{50}	2.1×10^{-4}	—
	(1.8×10^{-4})	
HIGH TOXICITY		−1.005[b]
		(0.494)
NO REFERENCE DOSE	−1.867[b]	−1.840[b]
	(0.869)	(0.817)
REFERENCE DOSE	21.27	20.67
	(18.63)	(17.21)

Panel C. Effect of change in variable from 0 to 1

Variable	Model 1	Model 2
SYNTHETIC	0.13	0.12
NOT CARCINOGENIC	−0.35	−0.01
HIGH TOXICITY	—	−0.21
NO REFERENCE DOSE	−0.41	−0.39

Panel D. Effect of change in variable from 0 to mean value.

Variable	Model 1	Model 2
RATS TD_{50}	0.01	—
REFERENCE DOSE	2.90	2.76

Note: Standard deviations for means and asymptotic standard errors for parameter estimates are in parentheses; t-tests are two-tailed.

[a]Significance level = 0.10.

[b]Significance level = 0.05.

[c]Significance level = 0.01.

negative effect on regulation. Cancer test results that indicate high toxicity lead to a probability of regulation that is −0.21 smaller than for less toxic chemicals. The rats' TD_{50} value, which is the continuous cancer risk measure, does not significantly influence the FDA regulation probability.

The GRAS designation, "Generally Regarded as Safe," was created by the FDA after the passage of the Delaney Clause to allow a loophole for not testing familiar additives. The substances qualifying for this status either were used in many different foods without suspicion of toxicity prior to 1958, or were more recent substances which had been demonstrated safe in lab tests for several other uses. Examples of GRAS substances are ethanol, formaldehyde, and FD&C Blue #1.

Table 6 (panel A) shows the regression results for the determinants of GRAS designation. Toxicity is not a factor in the model using the high-toxicity variable. The model using the continuous TD_{50} variable leads to the conclusion that substances with lower quantified cancer potency in rodents are significantly

Table 6. Food and Drug Administration (FDA) affirmation of substances as Generally Regarded as Safe (GRAS).

Panel A. Logit regression results for probability GRAS = 1.

	Coefficient (asymptotic standard error)	
Variable	Model 1	Model 2
INTERCEPT	−1.733[b]	−1.163
	(0.753)	(0.813)
SYNTHETIC	−1.488[c]	−1.501[c]
	(0.428)	(0.426)
NOT CARCINOGENIC	−2.083	0.793
	(1.998)	(0.542)
RATS TD_{50}	3.5×10^{-4}[a]	—
	(2.1×10^{-4})	
HIGH TOXICITY	—	−0.840
		(0.781)
NO REFERENCE DOSE	−0.214	−0.179
	(0.648)	(0.644)
REFERENCE DOSE	2.047	1.914
	(1.795)	(1.864)

Panel B. Effect of change in variable from 0 to 1

Variable	Model 1	Model 2
SYNTHETIC	−0.16	−0.16
NOT CARCINOGENIC	−0.22	0.08
HIGH TOXICITY	—	−0.09
NO REFERENCE DOSE	−0.02	0.02

Panel C. Effect of change in variable from 0 to mean value

Variable	Model 1	Model 2
RATS TD_{50}	0.01	—
REFERENCE DOSE	0.13	0.13

Note: Standard deviations for means and asymptotic standard errors for parameter estimates are in parentheses; t-tests are two-tailed.

[a]Significance level = 0.10.
[b]Significance level = 0.05.
[c]Significance level = 0.01.

more likely to be regarded as safe, as would be expected. *SYNTHETIC* substances are far less likely to be declared GRAS, a finding which affirms the results in Table 5.[21] As Table 6 (panel B) reveals, *SYNTHETIC* substances are about 16 percentage points less likely to be GRAS, after controlling for toxicity. This finding echoes the summary statistics, which indicate that 30 percent (25 of 83) of natural substances under FDA jurisdiction in the database were GRAS, while less than 10 percent of the relevant synthetic substances were so named (10 of 110). *NOT CARCINOGENIC* substances are GRAS about 24 percent (26 of 107) of the time, while only about 10 percent (9 of 86) of rat tumorigens are GRAS.

The results for the FDA are quite striking. The influence of the Delaney Clause that requires the FDA to ban all food additives for which there is evidence of carcinogenicity as well as other practices of the agency lead to a disturbing pattern of regulation. For the sample of chemicals within the agency's domain, the FDA is more likely to regulate synthetic chemicals than nonsynthetic chemicals. This synthetic risk bias holds even after controlling for different measures of the potency of the evidence of carcinogenicity. The more novel result is that risks that are more consequential in terms of their evidence of cancer potency are in fact less likely to be regulated. The pattern of regulation is the opposite of what one would expect if the agency targeted chemicals for regulation based on the magnitude of the risk rather than the character of the chemical.[22]

EPA Regulation

The pattern for EPA regulation is quite different. In terms of mean effects, the results in Table 7 (panel A) indicate no significant differences between synthetic and nonsynthetic chemicals in terms of the probability of regulation. Moreover, the risk potency variables perform in the manner one would expect if more serious risks are more likely to be regulated. Regulated chemicals are 15 percentage points less likely to be nontumorigenic and 19 percentage points more likely to be highly toxic. The rats' TD_{50} value is 70 percent lower for chemicals that are regulated than for those that are not, which is the pattern one would expect, because for more dangerous chemicals a lower dosage is required to induce tumor formation. Unregulated chemicals are more likely to have no reference dose that has been found to be toxic.

The same overall patterns of influence are borne out in the regression estimates in Table 7 (panel B). The synthetic risk variable does not have a statistically significant effect on the probability of regulation at the usual significance levels, and the point estimate of the effect is only 0.01. Highly toxic chemicals based on the cancer tests have a 0.23 higher probability of regulation. In the first equation, there is a -0.24 lower probability of regulation if there is no evidence of carcinogenicity. There is also a mean effect of the rats' TD_{50} value of -0.08. These two equations are quite consistent both in terms of the directions of influence as well as the magnitudes of the effects. Unlike the FDA, EPA regulations are not responsive to the synthetic character of the risk, but they do respond to the magnitude of the risk in the manner one would

[21] Unlike the results for FDA regulation, which demonstrate a synthetic bias when considering either all substances over which the agency has jurisdiction or just the subset of food exposures, the significance of the SYNTHETIC variable does not hold for the subsample of foods. This is perhaps explained by the smaller sample size in the food-only regression.

[22] The inverted sign on toxicity values could be affected by the self-selection caused by the licensing scheme, as discussed earlier. However, self-selection would not affect the results of the GRAS analysis. Synthetic substances are found to be overregulated by either approach.

Table 7. Environmental Protection Agency (EPA) Regulation.

Panel A. Variable means conditional upon whether the substance is regulated by the EPA

Variable	EPA Regulation = 1 (N = 186)	EPA Regulation = 0 (N = 179)
SYNTHETIC	0.753	0.709
	(0.433)	(0.455)
NOT CARCINOGENIC	0.430[c]	0.581[c]
	(0.496)	(0.495)
RATS TD_{50}	160.1[b]	537.3[b]
(N = 106, 75)	(348.7)	(1454.5)
HIGH TOXICITY	0.334[c]	0.145[c]
	(0.476)	(0.353)
NO REFERENCE DOSE	0.645[c]	0.983[c]
	(0.480)	(0.129)
REFERENCE DOSE	0.657	0.044
(N = 66, 3)	(3.734)	(0.050)

Panel B. Logit regression results for probability that EPA REGULATION = 1

	coefficient (asymptotic standard error)	
Variable	Model 1	Model 2
INTERCEPT	3.989[c]	3.073[c]
	(0.734)	(0.733)
SYNTHETIC	0.051	0.026
	(0.274)	(0.277)
NOT CARCINOGENIC	−1.319[c]	−0.408
	(0.264)	(0.300)
RATS TD_{50}	-1.3×10^{-3}[b]	—
	(5.5×10^{-4})	
HIGH TOXICITY		0.303[c]
		(0.335)
NO REFERENCE DOSE	−5.005	−4.944
	(3.242)	(3.144)
REFERENCE DOSE	2.102	2.042
	(0.734)	(5.273)

Panel C. Effect of change in variable from 0 to 1

Variable	Model 1	Model 2
SYNTHETIC	0.01	0.01
NOT CARCINOGENIC	−0.24	−0.07
HIGH TOXICITY	—	0.23
NO REFERENCE DOSE	−0.92	−0.89

Panel D. Effect of change in variable from 0 to mean value

Variable	Model 1	Model 2
RATS TD_{50}	−0.08	—
REFERENCE DOSE	0.24	0.23

Note: Standard deviations for means and asymptotic standard errors for parameter estimates are in parentheses; t-tests are two-tailed.

[a]Significance level = 0.10.

[b]Significance level = 0.05.

[c]Significance level = 0.01.

expect if the objective of government policy is to target more potent risks for regulation.

Twenty-two percent of the chemicals in the sample are regulated by OSHA. The mean effects in Table 8 (panel A) do not indicate any differences in the regulatory probability based on the synthetic character of the risk. The two risk variables that are significantly different across the two columns follow the patterns one would expect from regulatory policies targeted based on the magnitude of the risk. Unregulated chemicals are more likely to have chemical test results in which there is no evidence of carcinogenicity. Unregulated chemicals are also less likely to have high-toxicity values or to have reference dose exposure levels.

The regression results of Table 8 (panel B) indicate that the synthetic risk character has a statistically insignificant influence even after controlling for the other factors at work. The two most significant influences are the variables for whether a substance has been found to be carcinogenic or to have a reference dose level. The existence of a risk rather than its magnitude appears to be the main regulatory policy trigger although highly toxic rodent carcinogens are more likely to be regulated. The evidence linking regulatory policies to the magnitude of the risk is not as strong for OSHA as it is for the EPA. However, these two agencies share a common pattern of influence in that the synthetic character of the risk does not make regulation more likely.

CONCLUSIONS

How do the characteristics of a chemical affect its probability of regulation? Assuming all other aspects of regulatory contexts are similar, government agencies ideally should target the most consequential risks for their regulatory efforts.

Expanding upon the prior studies of dietary carcinogens by Ames, Profet, and Gold [1990b], Gold et al. [1992], and Viscusi [1995], this article has imposed a stronger test than inquiring whether some synthetic chemicals are more likely to be regulated than some nonsynthetic chemicals that pose lower risk. Using an exhaustive database of over 350 rat carcinogens rather than a smaller illustrative database, we have tested the respective roles of the synthetic character of the risk and the evidence of risk potency in agency risk management strategies. Based on results for a variety of toxicity and other measures, the FDA exhibits a very strong bias against synthetic chemicals. However, synthetic regulatory bias appears limited to the FDA, as neither the EPA nor OSHA exhibits a similar regulatory pattern.

Although the analysis has included measures of the risk level in part to control for the magnitude of the risk, the parameter estimates for the toxicity variables are of substantial interest in their own right. The regulations of the EPA are responsive to the risk level in that more potent carcinogens are more likely to be regulated. This performance runs counter to popular belief and is quite consistent with economists' policy prescriptions. For OSHA, the record is more mixed. Substances assigned toxicity values are regulated more heavily, as would be expected, but the quantified level does not seem to affect OSHA regulatory decisions. However, in the case of FDA regulations, one finds the opposite of the expected effect. The estimates using several risk measures indicated that less potent carcinogens are more likely to be regulated than more

Table 8. Occupational Safety and Health Administration (OSHA) Regulation.

Panel A. Variable means conditional upon whether the substance is regulated by OSHA

Variable	OSHA Regulation = 1 (N = 82)	OSHA Regulation = 0 (N = 283)
SYNTHETIC	0.695	0.742
	(0.463)	(0.438)
NOT CARCINOGENIC	0.378[c]	0.540[c]
	(0.488)	(0.499)
RATS TD_{50}	328.9	311.5
(N = 51, 130)	(1286.2)	(848.3)
HIGH TOXICITY	0.353[b]	0.216[b]
	(0.481)	(0.412)
NO REFERENCE DOSE	0.537[c]	0.890[c]
	(0.502)	(0.313)
REFERENCE DOSE	1.083	0.075
	(4.902)	(0.158)

Panel B. Logit regression results for probability that OSHA REGULATION = 1.

	Coefficient (asymptotic standard error)	
Variable	Model 1	Model 2
INTERCEPT	1.233[c]	0.932[a]
	(0.443)	(0.478)
SYNTHETIC	−0.515	−0.492
	(0.315)	(0.318)
NOT CARCINOGENIC	−1.332	−0.881[b]
	(1.726)	(0.365)
RATS TD_{50}	1.4×10^{-5}	—
	(1.8×10^{-4})	
HIGH TOXICITY		0.623[a]
		(0.368)
NO REFERENCE DOSE	−2.779[c]	−2.840[c]
	(0.572)	(0.577)
REFERENCE DOSE	0.945	0.964
	(0.867)	(0.875)

Panel C. Effect of change in variable from 0 to 1

Variable	Model 1	Model 2
SYNTHETIC	−0.07	−0.07
NOT CARCINOGENIC	−0.19	−0.12
HIGH TOXICITY	—	0.09
NO REFERENCE DOSE	−0.39	−0.39

Panel D. Effect of change in variable from 0 to mean value

Variable	Model 1	Model 2
RATS TD_{50}	0.001	—
REFERENCE DOSE	0.08	0.08

Note: Standard deviations for means and asymptotic standard errors for parameter estimates are in parentheses; t-tests are two-tailed.

[a]Significance level = 0.10.
[b]Significance level = 0.05.
[c]Significance level = 0.01.

potent carcinogens. Although the apparent pattern of focusing upon inconsequential risks might be a product of self-selection bias from the FDA licensing process, an alternative analysis of GRAS designations shows that the FDA gives more attention to synthetic substances than is merited by the risks they pose.

These biases mirror perception biases commonly exhibited in individual behavior. The result, however, is that the policies do not minimize the expected losses caused by the toxic effects of chemical substances.

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