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1988

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Mark A. Cleaves

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### Recommended Citation

Mark A. Cleaves, Assessment of Carcinogenic Risk and the Delaney Clause: The Search for a Better Standard, 2 J.L. & Health 173 (1987-1988)

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## Assessment of Carcinogenic Risk and the Delaney Clause: The Search for a Better Standard

Mark A. Cleaves\*

### I. Introduction

The determination of whether a chemical agent is a carcinogen is often a difficult task. Once carcinogenic potential is established, it is equally difficult to regulate the compound so that the public-at-large is not exposed to hazardous levels. When these agents are found in the food supply, the U.S. Food and Drug Administration (FDA) has the responsibility for the determination of safety.<sup>1</sup> Due to the complex nature of cancer and, at least until recently, uncertainties of its mechanism, the determinations of when a compound was safe under the Food, Drug and Cosmetic Act of 1938<sup>2</sup> and when it was carcinogenic were mutually exclusive events. Recent scientific developments require that the regulation of carcinogens by the FDA be re-evaluated.

Cancer is the uncontrolled or malignant growth of somatic cells which often results in the death of an organism.<sup>3</sup> As of 1978 it was the second largest killer in the U.S.<sup>4</sup> A causal relation between this disease and death has been established for centuries,<sup>5</sup> but it has only been within the last few decades that the prevalency and mechanism(s) of action have been elucidated. Tumor growth may be initiated by a variety of agents; one of the more important routes of exposure to these agents is via the ingestion of food.<sup>6</sup> This con-

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\*B.S. Toxicology, Northeastern University 1983; M.S. Pharmacology/Toxicology Northeastern University, 1987. J.D. Delaware Law School of Widener University, Wilmington, Delaware, 1987. The author would like to thank Dr. David R. Brown, Sc.D. and Rosann Reinhart for their helpful commentary on this article.

<sup>1</sup>Since 1906 federal law has forbidden adulterated and misbranded foods in interstate commerce. Federal Food and Drug Act of 1906, Pub. L. 59-384, 34 Stat. 768. (1906) (Repealed) The Food and Drug Administration was formerly part of the U.S. Department of Agriculture and was created to regulate food safety pursuant to the 1938 Food, Drug and Cosmetic Act, *infra* note 11.

<sup>2</sup>Federal Food Drug and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (1938) (current version at 21 U.S.C. § 321 (1970)); see also *infra* note 79 and accompanying text ("safe").

<sup>3</sup>See *infra* notes 202-216 and accompanying text (cancer process). Somatic cells are non-reproductive cells of the body which make up all of the bone and soft tissues. DORLAND'S POCKET MEDICAL DICTIONARY 133 (23rd ed. 1982).

<sup>4</sup>The Reader's Digest 1987 Almanac 454 (1987) (14th Am. ed. 1983). Cancer as a cause of mortality was second only to heart disease, its death rate 351.3 per 100,000 persons.

<sup>5</sup>Ramazzini in 1700 noted that nuns had a higher incident of breast cancer than other women. Pott also noted the occurrence of scrotal cancer in chimney sweeps in London, 1775. See also Chemical Carcinogens: A Review of the Science and Its Associated Principles, 50 Fed. Reg. 10,372 (1985) [hereinafter Principles]. See generally J. DOULL, C. KLASSEN, and M. AMDUR, CASARETT & DOULL'S TOXICOLOGY Ch. 6 (2d ed. 1980). [Hereinafter CASARETT & DOULL].

<sup>6</sup>See Principles *supra* note 5, at 10,383-10,387 (carcinogens may be of chemical, viral, physical or radiational origin, all of which may induce cancer and maybe found in food).

cern has lead Congress to adopt the strict standards found in the Food, Drug and Cosmetic Act,<sup>7</sup> which are meant to keep carcinogens out of the nation's food supply. These standards are found in three amendments dealing with food additives,<sup>8</sup> color additives<sup>9</sup> and drugs which are to be used in feed animals.<sup>10</sup> Each of these contain an anti-cancer provision known as the Delaney Clause,<sup>11</sup> named after the Chairman of the House Select Committee to Investigate the Use of Chemicals in Foods (1950-1953).<sup>12</sup> This legislation was passed due to the great public concern that foods and their contaminants were responsible for the deterioration of the nation's health.<sup>13</sup>

This article will focus upon the legislative history and subsequent case law dealing with the Delaney Clause and it will include the rationale and limitations of the provision. In order to regulate carcinogens one must have a clear understanding of the cancer processes. Therefore a brief discussion of the biological parameters involved is warranted. The purpose of this discussion is to find a more rational alternative to the Delaney Clause. The use of quantitative risk assessment as an approach to regulate carcinogens found in food is also discussed. By combining the purposes of the original (and current) statutory provisions with current technologies, a more efficient and workable regulation of carcinogens may be effectuated.

The Delaney Clause was enacted as a result of legitimate societal concerns and, while technologically faulty,<sup>14</sup> the amendment should not carelessly be dismissed. The original legislative intent may be better appreciated by tak-

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<sup>7</sup>*Supra* note 2

<sup>8</sup>Food Additive Amendments of 1958, Pub. L. No. 85-929 § 4, 72 Stat. 1784, 1786 (1958) (adding § 409(c)(3)(a) of the Act) (current version at 21 U.S.C. § 341 (1970)).

<sup>9</sup>Color Additive Amendments of 1960, Pub. L. No. 86-618, 74 Stat. 397 (1960) (adding § 706(b)(5)(B) of the Act) (current version at 21 U.S.C. § 376 (1970)).

<sup>10</sup>Animal Drug Amendments of 1968, Pub. L. No. 90-399, 82 Stat. 342 (1968) (adding § 512(d)(1)(H) of the Act) (current version at 21 U.S.C. § 360b (1970)).

<sup>11</sup>The "Delaney Clause" refers to specific portions of §§ 409, 706, and 512 of the Food, Drug and Cosmetic Act (FD&C Act), Pub. L. No. 75-717, 57 Stat. 1040 (1938) (Amended 1980). It derives its name from Congressman Delaney (D-N.Y.) who chaired the House Select Committee to Investigate the Use of Chemicals in Foods which was responsible for the enactment of the Clause. [Hereinafter Delaney unless otherwise specified] *Infra* note 46 and accompanying text (Delaney Clause text as amended in 1964).

<sup>12</sup>*Hearings on H.R. 74 Before the House Select Committee to Investigate the Use of Chemicals in Food Products*, 81st Cong., 2d Sess. (1951). These hearings were also the origin of the Pesticide Chemical Residue Amendments of 1954, Pub. L. No. 518, 68 Stat. 511 (1954) (current version at 21 U.S.C. § 346a (1970)).

<sup>13</sup>*See* Matson, *Scientific Judgement in Law and Regulation*, 15 FOOD DRUG COSM. L.J. 70, 74-75 (1960) (providing excerpts from House proceedings in 1959).

<sup>14</sup>*See infra* note 192 and accompanying text (scientific flaws of the Delaney Amendment).

ing into account current technologies in toxicology and other related fields. One such methodology, Quantitative risk assessment allows for the establishment of "Virtually Safe Doses" (VSD),<sup>15</sup> which are based on statistical evaluation of cancer processes. Although these procedures represent a new approach to the determination of safe levels of carcinogens, an evaluation of these approaches as they relate to scientific judgment and *priority setting* is required.<sup>16</sup> Quantitative risk assessment overcomes the scientific shortfalls of Delaney while protecting the American public from hazardous levels of carcinogenic substances.<sup>17</sup>

## II. Legislative History and Judicial Interpretation of the Delaney Clause

Since the beginning of this century the American public has been acutely aware of the hazards of contaminated food.<sup>18</sup> It was therefore no surprise that in 1906 the newly enacted Federal Food and Drug Act<sup>19</sup> contained a provision that made a food adulterated, and thus illegal, if it contained any poisonous or deleterious substance which rendered it injurious to health. This same provision is currently embodied in Section 402(a)(1) of the 1938 Federal Food, Drug and Cosmetics Act (FFDCA).<sup>20</sup>

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<sup>15</sup>"Virtually Safe Dose" has been defined as the dose corresponding to a suitably low level of risk and is defined in terms of an increase in tumors over the spontaneous background rate that is within an acceptable limit. Crump, Guess and Deal, *Confidence Intervals and Tests of Hypotheses Concerning Dose Response Relations Inferred from Animal Carcinogenicity Data*, 33 BIOMETRICS 437 (1977). See also text accompanying note 258.

<sup>16</sup>See *infra* note 228 and accompanying text (scientific judgment and risk assessment instead of an established zero tolerance).

<sup>17</sup>See *infra* note 29 and accompanying text (the original purpose of Delaney was to protect the American public from carcinogens in food). But see note 198 and accompanying text (impossibility of banning all carcinogens).

<sup>18</sup>Most of this awareness was brought about by Dr. Harvey Wiley who mobilized the famous "poison squad", which exposed young volunteers to food containing chemicals to observe adverse effects. See CASARETT & DOULL, *supra* note 5, at 593. As a result of this concern the doctrine of strict liability in tort began to emerge to provide a remedy for aggrieved parties that had suffered damages due to adulterated foods. See PROSSER AND KEETON, ON THE LAW OF TORTS, 690 (5th ed. 1985).

<sup>19</sup>See *supra* note 1 (1906 Act).

<sup>20</sup>21 U.S.C. § 342 (1938) (as amended 1970). There are numerous sources of the general legislative history of the FFDCA. See generally, Regier, *The Struggle for Federal Food and Drug Legislation*, 1 LAW & CONTEMP. PROBS. 3 (1933); U.S. GOV'T. PRINTING OFFICE, A BRIEF LEGISLATIVE HISTORY OF THE FOOD, DRUG AND COSMETIC ACT.

This Act, which expanded the 1906 Act, contained provisions to regulate naturally occurring, necessary and unavoidable constituents of foodstuffs.<sup>21</sup> These categories were set forth to distinguish between constituents that were "added" and those which were not.<sup>22</sup> It was unfortunate, however, that neither the 1906 nor the 1938 Act defined what "added" actually meant.<sup>23</sup>

As food technology advanced and awareness of the potential dangers of food additives grew, post-WWII America realized that more substantive regulation was required. By the early 1950's, not only had the detection of food contaminants become more feasible, but also the use of food additives, and chemical pesticides had increased.<sup>24</sup> In September, 1950, the House Select Committee to Investigate the Use of Chemicals in Foods held hearings, in which witness after witness testified to the horrors of the past years including the Elixir of Sulfanilamide and the "Ginger Jake" paralysis tragedies.<sup>25</sup> From the beginning it was clear that a new food-additives regulation was in the offing, but the hearings, nicknamed the "Delaney" Hearings after their Chairman, continued for the next two years.<sup>26</sup>

In 1958, after much debate, Section 409 was added to the FFDCA.<sup>27</sup> It established a premarket approval scheme containing a general safety clause

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<sup>21</sup>Provisions covering natural food constituents and unavoidable added constituents are contained in Food, Drug and Cosmetic Act §§ 402(a)(1), 406; 21 U.S.C. §§ 342, 346 (1938) (as amended 1970).

<sup>22</sup>*Id.* See U.S. v. Lexington Mill & Elevator Co., 232 U.S. 399 (1914). Section 402(a)(1) prohibits poisonous or deleterious substances which make food injurious to health. The Supreme Court found this to mean a reasonable certainty of no harm under the actual conditions of use.

<sup>23</sup>See Kopka, "If Mother Only Knew": *Regulating Carcinogens in Food Additives*, 31 MED. TRIAL TECH. Q. 273, 275 (1983). [Hereinafter *Regulating Food*].

<sup>24</sup>An example of the exponential growth in these chemicals from WWII to 1973 is exemplified by the growth of pesticides (680%) and flavors (400%). See NATIONAL SCIENCE FOUNDATION, CHEMICALS AND HEALTH (1973). See generally A. GOLDSTEIN, L. ARONOW AND S. KALMAN, PRINCIPLES OF DRUG ACTION 359-74 (2d ed. 1974) [hereinafter PRINCIPLES OF DRUG ACTION]. The first act concerning chemical regulation was the Pesticide Chemical Residue Amendments of 1954, see *supra* note 12.

<sup>25</sup>*Supra* note 14 (Delaney Hearings). In 1937, 105 out of 353 people died from ingesting sulfanilamide suspended in diethylene glycol, which was manufactured and sold by S. E. Massengill Co. Inadequate tests as to the toxicity of the solvent were to blame. See R. MERRILL AND P. HUTT, FOOD AND DRUG LAW 369 (1980); CASARETT & DOULL, *supra* note 5, at 483. In 1930 ginger extract adulterated with tri-orthocresyl phosphate was added as a flavoring agent to bootleg whiskey. Those who ingested it suffered progressive paralysis of the limbs. See CASARETT & DOULL, *supra* note 5, at 368.

<sup>26</sup>Congressman Delaney chaired the proceedings from 1950-1953. See generally Klienfeld, *The Delaney Proviso - Its History and Prospects*, 28 FOOD DRUG COSM. L.J. 556 (1973) (containing excerpts from the hearings). [Hereinafter *Delaney Proviso*].

<sup>27</sup>21 U.S.C. § 348 (as amended 1970), *supra* notes 8 and 11 with accompanying text (1958 Food Additive Amendments).

which requires that a food additive be found "safe" for its intended use.<sup>28</sup> This amendment was intended to mirror the national concern as to the presence of chemicals in food and it was designed to prevent all diseases and disabilities arising from food additives.

The Amendment, however, went much further. The final portion of Section 409 contained a clause that attempted to outlaw cancer at its source.<sup>29</sup> Representative Delaney was convinced by the testimony of the witnesses at the hearings that all carcinogens in food must be banned. Compounding Delaney's fears, was an unfortunate coincidence. The wife of one of his close aides had contracted cancer during the proceedings. Delaney felt that the need for an anti-cancer clause was exigent, and began to search for the proper provision.<sup>30</sup>

The origin of the Delaney Clause may be traced back to 1954. In Rome the International Union Against Cancer, gathered and drew important distinctions between reversible and irreversible chemical processes.<sup>31</sup> Scientists determined that threshold limits could be set for those chemicals which react reversibly in biological systems but that small doses of irreversibly-acting chemicals must be considered dangerous.<sup>32</sup> Two years later this concept was codified in an International Conference Against Cancer recommendation for proposed rules on food additives; the substance of the recommendation was seized upon by Chairman Delaney.<sup>33</sup>

The Union's findings, which considered even low doses dangerous, precluded the setting of any tolerances for these chemicals. This view was not espoused by all. In fact the FDA was not originally in favor of the clause. Perhaps it realized the scientific limitations of the concept or could foresee the problems of banning all food additives that cause cancer.

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<sup>28</sup>21 U.S.C. § 321(s). (1970) See *infra* text accompanying note 45 (definition of "food additive").

<sup>29</sup>Under § 409 a food additive would be deemed unsafe if based on relevant data the proponent fails to set forth conditions for its use. Safety is satisfied by meeting 201(s). Section 409 contains a specific anti-cancer clause, even though a finding of carcinogenicity would render the substance unsafe. 21 U.S.C. § 348(c)(3)(A) (as amended 1970).

<sup>30</sup>See *Delaney Proviso*, *supra* note 26, at 559.

<sup>31</sup>See Wade, *Delaney Anti-Cancer Clause: Scientists Debate on an Article of Faith*, 177 SCIENCE 588, 589 (1972). [Hereinafter *Article of Faith*].

<sup>32</sup>At the time the concept of irreversible one-hit effects of carcinogens was the only viable theory. Recent studies have since shown this to be not entirely true. See *infra* notes 202-249 (genetic vs. epigenetic carcinogens) and 211 (DNA Repair Mechanisms).

<sup>33</sup>In 1956 the International Conference Against Cancer recommended that "as a basis for active cancer prevention, the proper authorities of various countries promulgate and enact adequate rules and regulations prohibiting the addition to food of any substance having potential carcinogenicity." See *Article of Faith*, *supra* note 31, at 589.

The FDA noted that the first portion of the food additives amendment, known as the "General Safety Clause," and the second portion, the "Delaney Clause," were redundant.<sup>34</sup> It reasoned that if a chemical were found to be carcinogenic it could never be considered safe, and thus would be denied market approval.<sup>35</sup> This argument is flawed, however, because the General Safety Clause allows a risk-benefit analysis to set tolerances, while the Delaney Clause does not.<sup>36</sup> Nevertheless, the 1958 Food Additives Amendment was passed.<sup>37</sup>

Pursuant to Section 402(A)(1) of the 1938 Act, if a food contains "any poisonous or deleterious substance injurious to health" it is deemed adulterated and held illegal.<sup>38</sup> Under Section 402(A)(2)(a),<sup>39</sup> deleterious substances are pesticides,<sup>40</sup> food additives, color additives<sup>41</sup> and new animal drugs.<sup>42</sup> Prior to 1958, these sections required the agency to show that the levels of these substances found in food were not safe.<sup>43</sup> Section 409<sup>44</sup> of the 1958 Amendment specifically covers food additives. Food additives are defined by Section 201(s) of the Act as

[a]ny substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including

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<sup>34</sup>Section 409(c)(1)(A) of the Act sets out conditions for safe use of food additives. The FDA's position that the Delaney Clause would be redundant in light of the general safety clause is found in a letter written by then Assistant Secretary Elliot Richardson to the Delaney Committee. See Allera, *An Overview of How the FDA Regulates Carcinogens Under the Federal Food, Drug and Cosmetic Act*, 33 FOOD DRUG COSM. L.J. 59 (1978) [Hereinafter *Overview*]; *FDA Answers to Questions Submitted at Conference Cosponsored by FDA and FLI at Washington on November 16-17, 1959*, 15 FOOD DRUG COSM. L.J. 213 at 214 (1960) (In referring to Senate Report No. 2422, 85th Cong., 2d Sess. (1958), the FDA affirmed that its position was that "the bill reads and means the same with or without the inclusion of the (Delaney) Clause...").

<sup>35</sup>A finding that a substance was carcinogenic would in most cases, cause for it to be barred under the risk-benefit analysis of § 406 of the Act. Under § 409 with the Delaney Clause the risks automatically outweigh the benefits as a matter of law. *Accord Regulating Food*, *supra* note 23, at 277.

<sup>36</sup>*Id.* See 21 U.S.C. § 348(c)(4) (1970) (allows for setting of tolerances).

<sup>37</sup>*Supra* note 8.

<sup>38</sup>21 U.S.C. § 342 (as amended 1970) (adulterated food).

<sup>39</sup>*Id.* (enumeration of specific adulterants).

<sup>40</sup>Regulation of pesticides is covered under § 408 of the Act, the FDA, however, defers to U.S.D.A.'s setting and measuring of levels. 21 U.S.C. § 346a (as amended 1970).

<sup>41</sup>See *infra* notes 77-80 and accompanying text. (regulation of color additives).

<sup>42</sup>See *infra* notes 81-94 and accompanying text. (regulation of new animal drugs).

<sup>43</sup>The 1938 Act required that the FDA show that an intentionally added food substance was injurious to health. 21 U.S.C. § 342 (1938).

<sup>44</sup>21 U.S.C. § 348 (as amended 1970) (Food Additive Amendment of 1958).

any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be same under the conditions of its intended uses<sup>45</sup>

The Delaney Clause, Section 409(C)(3)(a) reads

. . . Provided, 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 or animal . . . .<sup>46</sup>

The Amendment is a pre-market screening device for food. It is specifically designed to prevent the addition of any substance that has been shown to induce cancer in man or laboratory animals.<sup>47</sup> The practical effect of this amendment, however, is to shift the burden of testing the additive and proving its safety to the proponent of its use.<sup>48</sup> More importantly, the Amendment had the effect of precluding the setting of safe tolerances for the amount of an additive deemed unsafe if it caused cancer.<sup>49</sup> The only issue left is to decide whether the additive did in fact cause cancer. This is accomplished after "a fair evaluation of the data before the Secretary".<sup>50</sup>

The scope of the Delaney Clause is limited by two exceptions to coverage. The first exception covers substances "generally recognized as safe" (GRAS)

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<sup>45</sup>21 U.S.C. 321(s) (1964).

<sup>46</sup>21 U.S.C. § 348 (as amended 1970).

<sup>47</sup>*Id.* Accord R. MERRILL AND P. HUTT, FOOD AND DRUG LAW 77 (1980). But see *infra* note 91 (New Animal Drug Amendments of 1962 and 1968 do allow such additions pursuant to specific conditions).

<sup>48</sup>See Chemical Compounds in Food Producing Animals: FDA Proposed Criteria and Procedures for Evaluating Assays for Carcinogenic Residues, 44 Fed. Reg. 17,070 (1979). [Hereinafter Evaluating Assays.]

<sup>49</sup>*Id.* This has been interpreted by some as the setting of a zero tolerance. Martin, *The Delaney Clause and Zero Risk Tolerance*, 34 FOOD DRUG COSM. L.J. 43 (1979) (Congressman Martin, then member of the Health Subcommittee of the House Ways and Means Committee, objected to the setting of such tolerances because many naturally occurring substances were in fact carcinogens).

<sup>50</sup>21 U.S.C. § 348(c)(3)(A) (1970).



by experts.<sup>51</sup> The second pertains to those substances that were sanctioned prior to 1958 by the FDA or U.S. Department of Agriculture (USDA), i.e. "prior sanctioned substances."<sup>52</sup>

The text of these exceptions appears to be straightforward, but in practice it is not. Substances generally recognized as safe include ingredients that have enjoyed a long history of use, such as salt, pepper, sugar, etc.<sup>53</sup> A GRAS classification may have been granted prior to 1958 or even after if the relevant data evaluated by the experts, proved the substance to be safe. If, however, new data shows that the ingredient is in fact a carcinogen then it will be taken off of the list.<sup>54</sup> Carcinogenicity precludes an expert from finding the ingredient safe; once this occurs the substance is deemed to be a food additive and is subject to Delaney prohibition.<sup>55</sup> Such is the case with Saccharin.<sup>56</sup> The FDA's "Grandfather Clause" of prior sanctioned substances precludes the use of Delaney, however, and new data that questions an ingredient's safety is evaluated according to Section 402(a)(1).<sup>57</sup>

It should also be noted that Delaney coverage does not extend to natural food constituents such as vitamins, minerals and animal biochemicals.<sup>58</sup> The FDA, has also held that unavoidable added food constituents are not subject to the Delaney Clause.<sup>59</sup> The FDA bases this determination on two assump-

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<sup>51</sup>21 U.S.C. § 321(s) (1970). The definition of "food additive" exempts substances generally recognized as safe by experts for their intended uses, as shown through scientific procedures.

<sup>52</sup>21 U.S.C. § 321(s)(4) (1970) (Prior sanctioned substances).

<sup>53</sup>General food categories are codified in 21 C.F.R. § 170.3(n) (1985); criteria for determining GRAS are found in 21 C.F.R. § 121.400 (1985).

<sup>54</sup>FDA periodically reevaluates data as to a substance's safety 21 C.F.R. § 170.35 (1985). If the data raises a substantial question as to safety but most of the scientific evidence favors safe use, the FDA may issue an interim food additive regulation until all the data is supplied. 21 C.F.R. § 180.1 (1985). There has been much scientific controversy surrounding the term "safe" as found in the GRAS provision. See Turner, *The Delaney Anticancer Clause: A Model Environmental Protection Law*, 24 VAND. L. REV. 889, 895-898 (1971). [Hereinafter *Protection Law*].

<sup>55</sup>*Supra* note 35 and accompanying text. Application for approval of use would then be withdrawn. See Cyclamate, Commissioner's Decision 45 Fed. Reg. 61,174 (1980) (Cyclamate salts withdrawn from GRAS list); *infra* note 218 and accompanying text.

<sup>56</sup>*Infra* notes 221-223 and accompanying text.

<sup>57</sup>21 C.F.R. §§ 181.1, 181.5 prior sanctioned ingredients are exempt from classifications as food additives, but not from other adulterations standards under § 402(a)(1); *Accord Overview*, *supra* note 34, at 75.

<sup>58</sup>*Supra* note 21 and accompanying text. Under Section 701(a) of the Act, FDA under its authority to promulgate regulations for efficient enforcement could ban a natural constituent. 21 U.S.C. § 371 (1970). See 21 C.F.R. § 189.180(b) (1985); 41 Fed. Reg. 19,207 (1976) (FDA ban of sassafras tea because safrole was found to be carcinogenic). *But see* U.S. v. Article of Food . . . Seelect Natural Herb Tea, C.A. No. 73-1370 (C.D. Cal. 1978) (manufacturer voluntarily withdrew claim after judge denied summary judgment).

<sup>59</sup>21 C.F.R. § 109 (1985).

tions. Although a substance may be "added" as within the meaning of Section 402(a)(1),<sup>60</sup> for Section 409 to attach, the compound must be functional upon addition to food; if the ingredient has no functional purpose, then Section 409 and Delaney do not apply.<sup>61</sup> Secondly, the FDA does not believe that the legislative intent was present for the food additives amendment to cover substances of this sort.<sup>62</sup> Like naturally occurring constituents, these substances are subject to Section 402(a)(1) treatment, but once "added" they may render the food "adulterated" and consequently are subject to Section 406 tolerance setting.<sup>63</sup> This section sets forth two criteria used to determine adulteration tolerances for poisonous compounds: 1) levels that will not pose a significant risk to public health and, 2) the extent to which contamination cannot be avoided by good manufacturing practices.<sup>64</sup> Implied by this section is the requirement that the FDA be able to measure the constituent; obviously the FDA cannot set a tolerance level that is beyond its ability to detect.<sup>65</sup>

It is clear that the food additive provision in the Delaney Clause was meant to circumvent the uncertainties present concerning carcinogens. The main thrust of this legislation was designed to insure that food was generally safe as well as free from carcinogens.<sup>66</sup> Two years after Congress passed the Food Additive Amendment the Delaney Committee proposed the Food Color Additive Amendment.<sup>67</sup>

By 1960, the controversy surrounding the Delaney Clause in the 1958 Amendment had had time to ferment. Disputes arose not only between poli-

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<sup>60</sup>21 U.S.C. § 342 (a)(1) (1970) (if a poisonous substance is not an "added" substance, then a food is not considered adulterated under the clause.)

<sup>61</sup>21 U.S.C. § 348(c)(4)(B) (1970) (Provision allows no regulation if "data do not establish that such use would accomplish the intended physical or other technical effect"); 21 C.F.R. 170.30 (1985).

<sup>62</sup>S. Rep. No. 2422, 85th Cong. 2d. Sess., *reprinted in* 1950 U.S. CODE CONG. AND ADMIN. NEWS 5300 (Food Additives Amendments of 1958. Functional requirement for additive to be approved).

<sup>63</sup>This mechanism avoids Delaney. Even though the substance is considered added and is found to be carcinogenic it is regulated by the risk-benefit analysis of § 406 of the Act rather than § 409. See 21 U.S.C. § 342(a)(2)(A) (1970) (food is adulterated if found unsafe under § 406). But see *supra* note 55 and accompanying text. (Thus it would seem that all carcinogenic substances are not always found unsafe.)

<sup>64</sup>21 U.S.C. § 346 (1970).

<sup>65</sup>*Infra* note 170 and accompanying text (Sensitivity of method to detect low levels of hazardous substances).

<sup>66</sup>*Accord Protection Law, supra* note 54, at 902.

<sup>67</sup>*Supra* note 9. (Color Amendments of 1960).

ticians and scientists, but also among scientists.<sup>66</sup> The National Academy of Science (NAS) was anti-Delaney whereas the National Cancer Institute (NCI) was firmly pro-Delaney.<sup>69</sup> This conflict was fueled by conflicting reports by both groups.<sup>70</sup> The NCI voiced legitimate concerns as to the uncertainties of setting tolerances for known carcinogens.<sup>71</sup> Extensive evaluation of data and current theories of carcinogenesis lead to a NAS Food Protection Committee report on food additives which concluded that *per se* regulation of carcinogens was inappropriate.<sup>72</sup> Despite the fact that this report was thorough and scientifically valid (and still considered so today) allegations of bias, weighed heavily against the report.<sup>73</sup> Throughout the hearings, these conflicts continued and did little to promote rational decision-making.<sup>74</sup>

Because of the uncertainties in the cancer process and the persisting societal fear of the disease, the Food Color Amendment contained a Delaney Clause.<sup>75</sup> The Amendment as enacted is basically the same as the 1958 Amendment, in that the proponent of the additive still had to prove its non-carcinogenic character.<sup>76</sup> To make such determinations the Amendment employs an *ad hoc* scientific advisory committee.<sup>77</sup> The purpose of the committee, convened by the Secretary or an adversely affected party, is to resolve Delaney questions. It does not mitigate Delaney prohibition of a color additive, but supplements data to aid in the Secretary's determination.<sup>78</sup> There is no GRAS listing however. Instead, a "provisional listing" of the additive is

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<sup>66</sup>See generally Hutt, *Public Policy Issues in Regulating Carcinogens in Food*, 33 FOOD DRUG COSM. L.J. 541 (1978); *Article of Faith*, *supra* note 31, at 589 (citing excerpts from hearings and discussion of NCI/NAS conflict).

<sup>69</sup>*Article of Faith*, *supra* note 31, at 589.

<sup>70</sup>*Id.*

<sup>71</sup>H.R. Rep. No. 1761, 86th Cong. 2d Sess., reprinted in 1960 U.S. CODE CONG. AND ADMIN. NEWS2887 (Color Additive Amendments of 1960 - role of certain chemical and physical agents in the causation of cancer).

<sup>72</sup>Subcommittee on Carcinogenesis, Food Protection Committee, Food and Nutrition Board, NAS-NRC, *Problems in the Evaluation of Carcinogenic Hazard from Use of Food Additives* 21 CANCER RES. 429 (1961).

<sup>73</sup>See *Article of Faith*, *supra* note 31, at 589.

<sup>74</sup>*Id.*

<sup>75</sup>See *infra* note 86 (color additives amendment for public protection but carcinogenic additives should be allowed where residues do not occur in the edible portions of animal products).

<sup>76</sup>21 U.S.C. § 378(b)(5)(B) (1970) (Anti-cancer Clause).

<sup>77</sup>21 U.S.C. § 376(b)(5)(c)(i) (1970) (allows for advisory committee review of data upon petition from Secretary or petitioner). This advisory committee is limited to review only as to the cancer issue and not free to deal with "any question of fact". See H.R. Rep. No. 6747, 85th Cong. 1st Sess. (1957) (similar restrictions are placed on the committee sanctioned by Pesticide Amendment of 1954).

<sup>78</sup>*Id.*

allowed to the extent consistent with public health until such time that determinations can be made as to its safety.<sup>79</sup> Thus, colors provisionally listed are technically outside of the Delaney Clause.<sup>80</sup>

During the hearings for the Food Colors Additive Amendment the Secretary of the Department of Health, Education and Welfare (HEW) expressed concern over the scope of the anti-cancer clause and wanted it modified to cover additives to animal feeds and animal drugs.<sup>81</sup> Although unsuccessful in 1960, this concern remained. The livestock industry was distraught because following the 1958 Food Additive Amendment, the FDA allowed the use of diethylstilbestrol (DES) in sheep and cattle but denied approval for new uses of the drug.<sup>82</sup> Section 201(u), which defines "safe", expressly covers the health of both man and animal.<sup>83</sup> Within the purview of Delaney, Congress recognized the potential adverse effects on humans from animal drug residues in animal products.<sup>84</sup>

In 1962 the Delaney Clause was added to a bill regarding FDA regulation and approval of new animal drugs.<sup>85</sup> The Senate passed over the provision without changes, but the House Committee on Interstate and Foreign Commerce made technical modifications that clarified its purpose and scope.<sup>86</sup> Included were clauses that allow for use of the additive if it did not adversely affect the animal and if no drug residues were found (by methods prescribed by the Secretary) on any edible product of the animal.<sup>87</sup> This clause became

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<sup>79</sup>*Id.*

<sup>80</sup>Color Additive Amendments of 1960, Pub. L. No. 86-618, § 203, tit. II, 74 Stat. 397; (1960). (Mandating provisional listings of commercially established colors).

<sup>81</sup>See Evaluating Assays *supra* note 48, at 17,072.

<sup>82</sup>Diethylstilbestrol is an anabolic steroid used primarily to promote growth and fatten livestock. It was first approved for use in premixed animal feeds in 1954 and later as a sustained-release implant in 1955. Due to the 1958 Food Additive Amendments, no new animal drug applications were approved by the FDA. See S. Rep. U.S. 1744, 87 Cong. 2d Sess., reprinted in 1962 U.S. CODE CONG. AND ADMIN. NEWS 2884 (Drug Amendments of 1962).

<sup>83</sup>21 U.S.C. § 321(u) (1970) ("the term 'Safe' . . . has reference to the health of man or animal").

<sup>84</sup>See Evaluating Assays, *supra* note 48, at 17,072. In passing §§ 409 and 706 of the Act Congress sought to recognize that animal drug residues would end up in man's food supply. FDA interpreted these provisions as forbidding it from approving the use of animal drugs thought to be carcinogenic.

<sup>85</sup>Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780, 21 U.S.C. § 360b(d)(1)(H) (1962).

<sup>86</sup>*Supra* note 71 and accompanying text (these modifications allowed DES to be used in the livestock industry).

<sup>87</sup>Official Methods for Detection, Identification and Measurement of DES Residues, 28 Fed. Reg. 1,507 (1963). These were changed several times, current criteria are found in Evaluating Assays, *supra* note 48. Revised threshold assessment guidelines are found in 47 Fed. Reg. 4,973 (1982).

known as the DES Proviso.<sup>88</sup> Pro- and anti-Delaney forces seized upon the opportunity to exchange views as to the proper method of regulating carcinogenic substances.<sup>89</sup>

Due to unprecedented growth in the animal feed and drug industries,<sup>90</sup> there was a move to consolidate the FFDCA provisions regulating the pre-marketing approval of animal drugs and feed additives.<sup>91</sup> In 1968 the Animal Drug Amendments under Section 512(d)(1)(H) were passed.<sup>92</sup> This amendment also contained an anti-cancer clause with "DES Proviso" attached:

(H) such drug induces cancer when ingested by man or animal or, after tests which are appropriate for the evaluation of the safety of such drug, induces cancer in man or animal, except that the following provisions of this subparagraph shall not apply with respect to such drug if the Secretary finds that, under the conditions of use specified in proposed labeling and reasonably certain to be followed in practice (i) such drug will not adversely affect the animals for which it is intended, and (ii) no residue of such drug will be found (by methods of examination and prescribed or approved by the Secretary by regulations, which regulations shall not be subject to subsections (c), (d), and (h)), in any edible portion of such animals after slaughter or in any food yielded by or derived from the living animals . . . .<sup>93</sup>

This clause followed the Congressional intent of the 1962 New Animal Drug Amendment and continued to allow the FDA to vigorously regulate new animal drugs.<sup>94</sup>

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<sup>88</sup>See 108 CONG. REC. 19,916-19,920 (1962).

<sup>89</sup>Representative Leonor K. Sullivan (D-MO) protested that this proviso would "weaken instead of strengthen consumer protection". Senator H. Humphrey (D-MN) noted that the full vigor of the Delaney Clause had been preserved.

<sup>90</sup>See Chemicals and Health, National Science Foundation (1973) (listing over 40 common animal drugs and feed additives).

<sup>91</sup>In 1968 Congress consolidated §§ 409, 505, and 507 which dealt with premarketing approval of drugs. Consequently the animal drug amendments were added under 512(d)(1)(H) of the Act. 21 U.S.C. § 360b(d)(1)(H) (1968).

<sup>92</sup>*Id.*

<sup>93</sup>*Id.*

<sup>94</sup>See S. Rep. No. 1308, 90th Cong. 2d Sess., reprinted in 1968 U.S. CODE CONG. AND ADMIN. NEWS 2607 (annual Drug Amendments of 1968. Delaney anticancer prohibition and the FDA authority to be maintained).

It must be preliminarily noted that the Delaney Amendment is seldom used to ban the food ingredients which it is meant to regulate.<sup>95</sup> This is because a positive indication of cancer induction must be found in order for Delaney to attach.<sup>96</sup> While this is not impossible, the FDA has typically performed safety evaluations according to the General Safety Clause of Section 409.<sup>97</sup> Since its enactment, FDA has used the Amendment only in three instances.<sup>98</sup>

From 1969-1983 Congress said little about the regulation of carcinogens in food and let the FDA, via its rulemaking powers, implement regulations.<sup>99</sup> During this time, however, the judiciary kept busy with litigation arising from these regulations. By far, most of the controversy surrounds the use of diethylstilbestrol in feed animals.<sup>100</sup>

Before examining case law, however, it would be useful to review FDA interpretation of Section 512(d)(1)(H) which deals with additives given to animals.<sup>101</sup> This provision is capable of multiple interpretations.<sup>102</sup> Those in

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<sup>95</sup>Prior to the 1958 Food Additive Amendments FDA had already removed food ingredients suspected to be carcinogenic. In 1950 the artificial sweeteners Dulcin and P-4000 were banned. 15 Fed. Reg. 321 (1950). In 1954 the use of the drug Coumarin in food was banned. 19 Fed. Reg. 1,239 (1954). After enactment of the anticancer clause it has been rarely used. It has been used in 1967 and 1969 to ban cyclamates 32 Fed. Reg. 5,675 (1967), 34 Fed. Reg. 17,063 (1969); and in 1977 to ban Saccharin, 42 Fed. Reg. 19,996 (1977). Instead FDA has opted to use the general safety clause to ban carcinogens, e.g. 25 Fed. Reg. 12,412 (1960) (Safrole); *Bell v. Goddard*, 366 F.2d 177 (7th Cir. 1966) (DES in Caponette poultry); 43 Fed. Reg. 17,063 (1969) (Cyclamates); *Certified Color Mfgs. v. Matthews*, 593 F.2d 284 (D.C. Cir. 1977) (Red Dye No. 2).

<sup>96</sup>In all anticancer provisions the substance must be shown to induce cancer in man or animals, these provisions allow no room for suspicion. Because the general safety clause employs a risk-benefit test a substance's carcinogenic potential is also a factor. See 21 U.S.C. §§ 348(c)(3)(A) (1970), 376(b)(5)(B) (1960) and 360b(d)(1)(H) (1968) (Anticancer Clauses); 21 U.S.C. § 346 (1970) (use of risk-benefit test in setting tolerances pursuant to 402(a)).

<sup>97</sup>See *supra* note 11.

<sup>98</sup>See generally *supra* note 95.

<sup>99</sup>21 U.S.C. § 371 (1976) (General Administration Provisions - regulations, rulemaking and hearings).

<sup>100</sup>See *Bell v. Goddard*, 366 F.2d 177 (7th Cir. 1966) (use of DES in Caponette poultry); *Hess & Clark, Division of Rhodia, Inc. v. FDA*, 495 F.2d 975 (D.C. Cir. 1974) (DES implants); *Chemtron Corporation v. U.S. Dept. of Health, Education and Welfare*, 495 F.2d 995 (D.C. Cir. 1974) (use of DES in livestock feed mixes); *Animal Health Institute v. FDA*, [1978 Transfer Binder] Food Drug Cosm. L. Rep. (CCH) ¶ 38,154 at 38,557 (D.D.C. Feb. 8, 1978) (adequacy of notice and comment rulemaking regarding DES detection methods); *Rhone-Poulenc, Inc., Hess & Clark Div. v. FDA*, 636 F.2d 750 (D.C. Cir. 1980) (substantial evidence showing that DES was unsafe).

<sup>101</sup>*Supra* notes 91-93 and accompanying text (text of § 512(d)(1)(H)).

<sup>102</sup>See *Evaluating Assays*, *supra* note 48, at 17,073; *infra* text accompanying note 167 (discussion of reproposal of SOM Regulations).

favor of more progressive interpretation would like to believe that the FDA would have to absolutely prove the presence of trace residues before banning the product.<sup>103</sup> This interpretation is flawed in many respects especially since it appears contrary to congressional intent. Scientifically, such proof is impossible, because in most instances there would be traces of the chemical residue no matter how minute in the animal. Such residues were beyond the detection of FDA's analytical methods until only recently.<sup>104</sup>

Furthermore, it is contrary to congressional intent to interpret the provision in that manner. When Congress enacted the provision it used the word "found" instead of "occur" or "remain", this evidenced reliance on detectability and not absolute presence.<sup>105</sup> The term "no residue" is given the meaning no detectable residue.<sup>106</sup> Congress also limited the provision to "condition of use", thus allowing compounds to remain on the market even if residues were found, but not from intentional addition.<sup>107</sup> The more probable interpretation of the provision is that if a carcinogenic compound used in animals is not detected by FDA in assays prescribed, the compound is free from Delaney coverage.<sup>108</sup>

The first litigation to involve the DES Proviso was *Bell v. Goddard*.<sup>109</sup> In *Bell*, a manufacturer of DES implants for the *Caponette poultry industry* contended that FDA suspension of his New Annual Drug Application (NADA) was improper. At the time the carcinogenic affect of DES was not completely

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<sup>103</sup>A literal reading could show § 512 to read "... if the Secretary finds that ... no residue of such drug will be found." See U.S.C. § 360b(d)(1)(H) (1970).

<sup>104</sup>*Supra* note 102 and accompanying text (discussion of latest SOM detection limits).

<sup>105</sup>See 21 U.S.C. § 360b(d)(1)(H) (1970) (text); Evaluating Assays, *supra* note 48, at 17,073. (Noting statutory construction).

<sup>106</sup>*Id.*

<sup>107</sup>See 21 U.S.C. § 360b(d)(1)(H) (1970) (text). Once a chemical is deposited in the environment it remains there until picked up by another organism. Thus environmental contaminants such as DDT and even DES that were once used so pesticides or animal drugs may show up as trace chemicals even though never intentionally given to the animals. See generally CASARETT & DOULL, *supra* note 5, at 601.

This conclusion was expressed by Senator Kefauver during the new Drug Amendment Hearings in 1962:

The provision stipulates that the anti-cancer proviso of existing law shall not apply with respect to the use of a substance — for example, a veterinary drug — as an ingredient of feed for animals which are raised for food production if the Secretary finds . . . that no residue of the additive will be found after slaughter or in any food product of the living animal — such as milk or eggs. 108 Cong. Rec. 20,869 (1962).

<sup>108</sup>See *Hess & Clark, Div. of Rhodia, Inc. v. FDA*, 495 F.2d 975, 980 (D.C. Cir. 1974); *Chemtron Corporation v. Dep't of Health Educ. and Welfare*, 495 F.2d 995, 999 (D.C. Cir. 1974).

<sup>109</sup>366 F.2d 177 (7th Cir. 1966).

known.<sup>110</sup> The manufacturer contended that the FDA knew about DES' propensity to cause cancer, but it delayed a finding that DES was safe as used to employ the Delaney Clause retroactively.<sup>111</sup> The court found that the FDA had shown that DES was unsafe, and could wait until all the data was in.<sup>112</sup> The FDA chose to ban DES based on its unsafe nature as prescribed by Section 505(e) which pertains to new drugs.<sup>113</sup> Bell illustrates two points concerning the FDA's regulation of drugs and additives. First, the FDA has broad discretion as to what provisions to utilize in setting tolerances or banning such compounds.<sup>114</sup> Second, it shows that no matter how safe the substance may be in relative terms of use, a finding of carcinogenic potential may render it unsafe.<sup>115</sup>

The "DES" Proviso was again scrutinized in 1974 in *Hess & Clark, Inc. Division of Rhodia v. FDA*.<sup>116</sup> The FDA had once again withdrawn the manufacturer's NADA for DES implants. The court recognized that the DES Proviso carved out an exception to Delaney, and that the permissible limits of DES were to be based on detectability in edible animal tissue.<sup>117</sup> (Since *Bell*, the USDA had begun to utilize gas-liquid chromatography to detect residues.<sup>118</sup> This method is much more accurate and quicker than the previously used mouse-uterine test (0.5 ppb vs. 2 ppb).)<sup>119</sup> The 1968 Amendment required a hearing before a compound could be withdrawn from the market.<sup>120</sup> The

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<sup>110</sup>It was not until 1971 that the use of DES was discovered to cause an increased incidence of vaginal carcinoma after being administered to the mothers in order to maintain a successful pregnancy. Greenwald, Barlow, Nasca and Burnett, *Vaginal Cancer After Maternal Treatment with Synthetic Estrogens*, 285 NEW ENG. J. MED. 390 (1971); Herbst, Kurman, Scully and Poskanzer, *Clear-Cell Adenocarcinoma of the Genital Tract in Young Females*, 287 NEW ENG. J. MED. 1259 (1972). There was some evidence that DES did cause cancer in animals. *Bell*, 366 F.2d at 179.

<sup>111</sup>*Bell*, 366 F.2d at 181.

<sup>112</sup>*Id.*

<sup>113</sup>Section 505(e) of the Act allows FDA to deny any unsafe drug access to the marketplace. 21 U.S.C. § 355(e) (1967).

<sup>114</sup>The FDA may use the general safety provisions or Delaney Clause and has often alternated between the two in regulating carcinogenic substances. See *supra* note 95 and accompanying text.

<sup>115</sup>It has been noted that Congress places a heavy burden upon an administrator to explain the basis for allowing the continued use of a carcinogenic substance. See *Environmental Defense Fund, Inc. v. Ruckelshaus*, 439 F.2d 584, 596 (D.C. Cir. 1971) (case involved DDT but mentioned the Delaney Amendment by name).

<sup>116</sup>495 F.2d 975 (D.C. Cir. 1974).

<sup>117</sup>*Id.* at 979

<sup>118</sup>*Id.*

<sup>119</sup>*Id.* at 979 n. 6 (GLC sensitivity).

<sup>120</sup>21 U.S.C. § 360(c)(3)(e) (1970) (notice and opportunity for Journal hearing).



FDA asked for and received materials from manufacturers concerning safety; based on this information it was decided that there was no genuine issue of fact and denied the hearing.<sup>121</sup>

The court found the FDA in error for two reasons. First, since the Act allows for summary withdrawal if the Secretary finds imminent danger to public health, the finding must be made by the Secretary and not delegated to the Commissioner.<sup>122</sup> The FDA had stated in its finding that the NADA withdrawal was a regulatory matter and that DES did not present a public health hazard.<sup>123</sup> The court also found error because the FDA should have given the manufacturers notice of the results and time to respond as required by due process of law.<sup>124</sup> Although tests were available to determine if there were DES residues present, the FDA was precluded from using the data because they had not yet been approved by the Secretary; the mouse-uterine test failed to detect these levels.<sup>125</sup>

Once again the FDA employed the General Safety Clause.<sup>126</sup> The court found that since the FDA desired to withdraw the drug, it had the initial burden of coming forward with evidence showing a link between the residue and safety.<sup>127</sup> The court then found that facts as to safety—which “inevitably means calculating whether the benefits which the drug produces outweigh the costs of its restricted use” — were not established by the FDA.<sup>128</sup> *Hess & Clark* did not, however, address the procedures which the FDA used to set assay requirements under the DES Proviso; the court implicitly accepted the FDA’s expertise in this area.<sup>129</sup> A companion case reaffirmed that the FDA’s notice and due process procedures were in error in denying a hearing on

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<sup>121</sup>37 Fed. Reg. 15,747 (1962); *Hess & Clark*, 495 F.2d at 980.

<sup>122</sup>The Secretary could *not* delegate the finding of “imminent hazard to the health of man”. 495 F.2d at 982, citing 21 U.S.C. § 360b(e)(1) (1970).

<sup>123</sup>38 Fed. Reg. 10,485, 10,488 (1973) (order withdrawing FDA approval of NADA’s for DES implants).

<sup>124</sup>*Hess & Clark*, 495 F.2d at 994.

<sup>125</sup>*Id.* at 991 (§ 512(d)(1)(H) specifically requires approval of method by the Secretary).

<sup>126</sup>*Id.* See 21 U.S.C. § 360b(e)(1)(B) (1969).

<sup>127</sup>*Hess & Clark*, 495 F.2d at 993. In a later decision, the same court found that the FDA had met its initial burden of coming forward with evidence of a substance’s safety, and that its conclusion was supported with substantial evidence. *Rhone-Poulenc, Inc., Hess & Clark Div. v. FDA*, 636 F.2d 750, 753 (D.C. Cir. 1980).

<sup>128</sup>495 F.2d at 993-4.

<sup>129</sup>*Id.* (Noting that the relationship between the residues and safety were based on the nature and amount of the residues not their detection methods).

DES feed pre-mixes.<sup>130</sup> These early cases reinforced the FDA's desire for procedures to alleviate uncertainties in evaluating and designating assays pursuant to the DES Proviso.

In 1973 the FDA published notice in the Federal Register to promulgate new assay rules; these were later codified in 1977.<sup>131</sup> These regulations, however, did not settle the DES controversy. The six-step review process, as proposed, incorporated the Mantel-Bryan paradigm which was designed to predict the risk of cancer due to low level exposure to carcinogens.<sup>132</sup> The final regulations contained significant innovations to the method.<sup>133</sup>

In *American Health Institute v. FDA*,<sup>134</sup> The American Health Institute (AHI) sought to stay the effective date of the regulations because proper rulemaking procedures employing notice and comment had not occurred. Specifically, AHI contended that the regulations were unlawful because they unnecessarily broadened the scope of the Delaney Clause and because they precluded the use of a compound unless an assay existed which was sensitive enough to detect residues at the theoretically (Mantel-Bryan) safe levels.<sup>135</sup> The court found the agency's notice and comment procedures, as well as its definition and explanation of the criteria and procedures for evaluation of carcinogenic residues, faulty.<sup>136</sup> The FDA promptly published proposed rules in the Federal Register which have collectively come to be

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<sup>130</sup>*Chemetron Corp. v. U.S. Dep't of Health Educ. & Welfare*, 495 F.2d 995 (D.C. Cir. 1974).

<sup>131</sup>42 Fed. Reg. 10,412 (1977) (Procedures for evaluation of assays used to assess risk of undetected residues).

<sup>132</sup>The Mantel-Bryan approach allows for the estimation of a level of a specific carcinogen that would lead to a non-detectable increase in cancer rates during experimentation. Mantel and Bryan, *Safety Testing of Carcinogenic Agents*, 27 J. NAT'L CANCER INST. 455 (1961) (General approach); Mantel, *Improved Mantel-Bryan Procedure for "Safety" Testing of Carcinogens*, 35 CANCER RESEARCH 865 (1975). See *infra* notes 270-71 and accompanying text (full discussion of basis of procedures). See *infra* notes 235-243 and accompanying text (Quantitative Risk Assessment procedures).

<sup>133</sup>Commissioner set forth proposed rules, using the method described in the 1961 Mantel and Bryan Paper for comment on July 19, 1973. 38 Fed. Reg. 19,226 (1973). Final regulations were promulgated February 22, 1977. 42 Fed. Reg. 10,412 (1977). These regulations, however, employed methods found in the 1975 Mantel and Bryan paper. See *supra* note 132.

<sup>134</sup>[Transfer Binder 1978] Food Drug Cosm. L. Rep. (CCH) ¶ 38,154 (D.D.C. Feb. 8, 1978). AHI claimed FDA violated § 551 of the Administrative Procedure Act which prescribes in formal notice and comment rulemaking.

<sup>135</sup>*Id.* at 38,563.

<sup>136</sup>*Id.* at 38,564. The court according to the standard of review set out in § 706(2)(B) of the Administrative Procedure Act found the FDA's procedures "arbitrary and capricious." See *Citizens To Preserve Overton Park v. Volpe*, 401 U.S. 402 (1971); *Burlington Trucklines v. U.S.*, 371 U.S. 156 (1962) (standards for review of agency rulemaking procedures).

known as the Sensitivity of Method (SOM) Proposal.<sup>137</sup> They contain elaborate procedures for evaluating carcinogenic risk, the technical aspects of which require a more extensive discussion of carcinogenesis.<sup>138</sup>

While litigation concerning new animal drugs has provided some insight into the scope of Delaney, litigation concerning the Colors Amendment<sup>139</sup> has also shed some light on the subject. Color additives have been more heavily scrutinized under Delaney than food additives or new animal drugs because they lack serious social benefits and are utilized merely as aesthetic agents.<sup>140</sup> In general FDA has been more active in banning carcinogenic color additives. In order for the Delaney Amendment to apply, the additive must adhere to the statutory definition; its primary purpose is to impart color to food, and not be exempted.<sup>141</sup> These determinations may be made by either the USDA or FDA.<sup>142</sup> Delaney coverage of these substances has been inconsistent. A 1976 case reaffirmed the doctrine that FDA has discretion in deciding to use Delaney or the General Safety Clause to ban a carcinogenic color additive.<sup>143</sup>

Beginning in 1979, the court's interpretation of the Delaney Clause in *Monsanto Company v. Kennedy*<sup>144</sup> began a movement toward a more realistic

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<sup>137</sup>Chemical Compounds in Food-Producing Animals, 44 Fed. Reg. 17,070 (1979) (rules establishing criteria to determine chemical residues in animal tissue): See Evaluating Assays, *supra* note 48. *Id.* See generally Norcross, *Sensitivity of Method - A Wave of the Future*, 35 FOOD DRUG COSM. L.J. 342 (1980); Dexler, *The Impact of Sensitivity of Method on Food Regulation*, 35 FOOD DRUG COSM. L.J. 349 (1980); Becker, *Sensitivity of Method - Legal Implications*, 35 FOOD DRUG COSM. L.J. 355 (1980). Those interested in examining the criteria should consult FDA's "Redbook" and Good Laboratory Practices regulations. See 21 C.F.R. Pt. 58 (1987).

<sup>138</sup>Chemical Compounds in Food-Producing Animals; availability of new threshold assessment criteria for guidelines, 47 Fed. Reg. 4,972 (1982) (notice of revised evaluation system). See Evaluating Assays *supra* note 48 and accompanying text (full discussion). See also *infra* note 217 and accompanying text.

<sup>139</sup>21 U.S.C. § 376 (1970).

<sup>140</sup>FDA has banned the use of many color additives such as carbon black (41 Fed. Reg. 41,857 (1976)), graphite (42 Fed. Reg. 60,734 (1977)), and FD&C Yellow No. 1 (42 Fed. Reg. 62,478 (1977)). It also has attempted to put warning labels on some coal-tar hair dyes. See 44 Fed. Reg. 59,513 (1979). Food additives are often used to preserve food for transport and longer shelf life, color additives are used mainly for their aesthetic values. Accord Matson, *Scientific Judgement in Law and Regulation*, 15 FOOD DRUG COSM. L.J. 70 (1960).

<sup>141</sup>Color additives are defined in 21 U.S.C. § 321(t) (1970) and do not include pesticides or substances that are added for purposes other than coloring. See 21 C.F.R. § 70.3(g) (1985) (purposes other than coloring).

<sup>142</sup>See *Public Citizen v. Foreman*, 471 F. Supp. 586, 594 (D.D.C. 1979) (court held that nitrite use in bacon was not primarily to fix color and pursuant to the Federal Meat Inspection Act, 21 U.S.C. § 621 (1907)(revised 1967), the U.S.D.A. had primary jurisdiction).

<sup>143</sup>*Certified Color Manufacturers v. Matthews*, 543 F.2d 284 (D.C. Cir. 1977) (termination of provisional listing of FD&C Red No. 2).

<sup>144</sup>613 F.2d 947 (D.C. Cir. 1979).

view of the Clause. The case arose after the Commissioner published regulations setting tolerance levels of acrylonitrile monomer in plastic beverage containers pursuant to the General Safety Clause.<sup>145</sup> The FDA projected that these levels would be exceeded by the manufacturer's product.<sup>146</sup> The manufacturer contended that the monomer left after formulation and curing was firmly bound and that it would not migrate from the container to the food under conditions of intended use.<sup>147</sup> The court found that the Commissioner did have the discretion to issue technology-forcing provisions when promulgating food safety regulations, but that FDA's projections were based on insufficient data.<sup>148</sup> More importantly, however, it found that the statutory definition of "food additive" could be satisfied by the second law of thermodynamics (i.e. diffusion).<sup>149</sup>

The *Monsanto* court set forth a two prong test consisting of component and safety elements.<sup>150</sup> First, the intended use of the substance must be reasonably expected to result in its becoming a component of the food.<sup>151</sup> Secondly, based on congressional intent, the amount to be found must be significant, i.e., not *de minimis*.<sup>152</sup> This does not require that the amount present be toxicologically significant, but that the level may even be based upon a prediction founded on reliable data.<sup>153</sup>

The finding of a *de minimis* standard for the definition of food additive immediately raised questions as to the viability of the Delaney *per se* or zero tolerance cancer prohibition.<sup>154</sup> The court's finding of inferred statutory in-

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<sup>145</sup>Acrylonitrile is used as a monomer in the making of plastics. It has been found to be carcinogenic. See CASARETT & DOULL, *supra* note 5, at 532. Indirect additives: Polymers, 42 Fed. Reg. 48,528 (1977). Commissioner originally set migratable (unpolymerized acrylonitrile) levels at 80 ppb; later, after it was learned that acrylonitrile was toxic to laboratory animals, its use in beverage containers was banned completely.

<sup>146</sup>*Monsanto*, 613 F.2d at 951.

<sup>147</sup>*Id.* at 953.

<sup>148</sup>*Id.*; see *infra* note 232 and accompanying text (technology-forcing procedures).

<sup>149</sup>613 F.2d at 955.

<sup>150</sup>*Id.*

<sup>151</sup>*Id.*

<sup>152</sup>*Id.* at 955 n. 26 (citing cases where statutes did not apply to *de minimis* situations).

<sup>153</sup>*Id.* Commissioner must base his decision on reliable data but has discretion to appraise the public health and welfare. If circumstances exist he may decline to regulate *de minimis* situations.

<sup>154</sup>Although *Monsanto* only dealt with the safety clause the court seemed to dispose of *de minimis* risk with such dispatch one wonders if the same argument could have been made for *de minimis* levels of carcinogenic food additives or drug residues left on edible tissue of animals. See *infra* notes 161-172 and accompanying text (FDA proposed to deal with drug residues).

tent against regulating insignificant levels runs contrary to the prior belief that Delaney would not tolerate any carcinogenic risk.

The *Monsanto* decision clearly begs the question, "Is the DES Proviso the only exception to Delaney?" Many commentators believe that it is not.<sup>155</sup> Analysis of the legislative history reveals inconsistencies, with scientists advocating that some sort of dose-response standard is required<sup>156</sup> and the rest of the population intimidated by the seemingly unconquerable cancer threat.<sup>157</sup> The underpinnings of the Delaney Clause are based on the conception that no threshold dose is able to be found for carcinogens.<sup>158</sup> A *de minimis* rule would seem to imply that there is. The FDA's use of Mantel-Bryan's model would also encourage this result.

If *Monsanto* did not lead to, it certainly contributed to, the 1982 publishing of the advanced notice of proposed rulemaking pertaining to food additives by the FDA.<sup>159</sup> The FDA notice set forth three approaches for comments. These were the constituent, *de minimis*, and sensitivity-of-method approaches.<sup>160</sup> The constituents approach would preclude application of the Delaney Clause based on the biologic reactivity of the whole additive as compared to its constituents: for Delaney to apply the additive on the whole would have to be found to induce cancer in animals.<sup>161</sup> Individual constituents would not be banned even if they are carcinogenic unless they render the whole additive carcinogenic. On a biological basis this approach in practice rules out indirect (epigenetic) carcinogens.<sup>162</sup> This approach also has a "functional component"; *i.e.*, only if the constituent is found to be functional will Delaney apply.<sup>163</sup> Of course, one of the major limitations of this approach deals with classification of constituents. In practice it is difficult to

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<sup>155</sup>See Merrill, *Risk-Benefit Decisionmaking by the Food and Drug Administration*, 45 GEO. WASH. L. REV. 994 (1977); Henteleff, "Modernizing" the Delaney Clause, 38 FOOD DRUG COSM. L.J. 147 (1983).

<sup>156</sup>*Supra* note 72 and accompanying text (NAS 1961 Report).

<sup>157</sup>*Supra* note 12 and accompanying text (1950-53 Delaney hearings).

<sup>158</sup>This concept is known as the "one-hit" theory of carcinogenesis. See *infra* note 201 and accompanying text.

<sup>159</sup>47 Fed. Reg. 14,464 (1982) (Revised policy for regulating carcinogenic chemicals in food and color additives).

<sup>160</sup>*Id.*

<sup>161</sup>An additive may contain many other substances besides the actual preservative, colorant or other functional component. These include residual reactants, unreacted intermediates, catalysts, solvents and other manufacturing aids; as well as products from co-reactions and chemical degradations. See 47 Fed. Reg. 14,464, 14,468 (1982).

<sup>162</sup>See *infra* notes 201-226 and accompanying text (mechanisms of carcinogenicity).

<sup>163</sup>Technically non functional substances found in food additives/colors would be considered "constituents" rather than "additives". 47 Fed. Reg. 14,464, 14,468 (1982).

determine which is functional and which is not; there is also the serious scientific consideration of how the additive biologically reacts once ingested.<sup>164</sup>

The second approach follows the *Monsanto* finding of *de minimis*: the Delaney Amendment would not apply if the level of the additive is so negligible that it presents no public health concern.<sup>165</sup> *De minimis* approaches have been used with other FFDCA provisions concerning adulteration.<sup>166</sup> This approach would seem to require some method of risk assessment to determine the *de minimis* level. This approach would attempt to negate flaws of the Delaney Amendment found in its original form.<sup>167</sup>

The third approach is based on the 1979 proposed regulations<sup>168</sup> and is derived from the DES Proviso.<sup>169</sup> The sensitivity-of-method approach has been touted by many, mainly because it is administratively workable and based upon a rather solid scientific foundation.<sup>170</sup> This approach incorporates a conservative maximum risk of cancer equal to one in one million over the lifetime of a human being.<sup>171</sup> The FDA also seems to favor this approach out of the three and has even revised the threshold assessment criteria from the previous regulations.<sup>172</sup> By announcing this proposed change in policy, the FDA has opened the door to changes regarding the regulation of carcinogens in food.

In 1983, Senator Orrin Hatch, Chairman of the Senate Labor and Human Resources Committee, presided over hearings that were designed to ad-

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<sup>164</sup>The most important consideration deals with the overall carcinogenic activity of the constituent. The constituent may act as a promoter, it may be carcinogenic alone, or it may have no impact on the carcinogenicity of the additive *per se*, but enhance the carcinogenicity of another compound. See Principles, *supra* note 5.; See also *Infra* note 207 and accompanying text (promoters and initiators).

<sup>165</sup>613 F.2d at 955; 47 Fed. Reg. at 14,467 (1982).

<sup>166</sup>See *U.S. v. 1,500 Cases More or Less Tomato Paste*, 236 F.2d 208, 215 (7th Cir. 1956) (insect fragments "were so low that they are regarded . . . as insignificant or of no consequence", using 402(a)(3)); *U.S. v. General Foods Corp.*, 446 F. Supp. 740 (N.D. N.Y.) in *aff'd* 591 F.2d 1332 (2d Cir. 1978) (presence of mold on food processing machinery was *de minimis*).

<sup>167</sup>See *supra* notes 188-223 and accompanying text.

<sup>168</sup>44 Fed. Reg. 17070 (1979) (SOM regulations); Evaluating Assay, *supra* note 48.

<sup>169</sup>*Supra* notes 91-93 and accompanying text.

<sup>170</sup>SOM is administratively workable because the substance would be deemed safe if its levels could not be measured, 44 Fed. Reg. 17,070 (1979). But current technology demonstrates that detection limits are now so low, that the compound is effectively banned.

<sup>171</sup>SOM uses the Mantel-Bryan Approach which utilizes a risk level of  $10^{-6}$  limit; i.e., the level at which one in one million people may be expected to contract cancer if exposed to the chemical. *Infra* note 270 and accompanying text.

<sup>172</sup>47 Fed. Reg. 4,972 (1982) (revised threshold criteria requiring the use of the most sensitive detection methods as a technology-forcing policy).

dress alternatives to the Delaney Amendment.<sup>173</sup> While the product of these meetings has yet to be fully appreciated, the fact that they were held is significant. After twenty-five years, the shortfalls of the Delaney Clause were finally being addressed.<sup>174</sup>

To further support the desire for a change in the regulation of carcinogens in food, the Sixth Circuit adopted the FDA's constituents approach in *Scott v. FDA*.<sup>175</sup> *Scott* dealt with the permanent listing and continued use of Green No. 5, which is manufactured from p-toluidine, a known carcinogen.<sup>176</sup> The court found that although the color may contain traces of its carcinogenic intermediate and impurities, the additive as a whole should be tested.<sup>177</sup> It also found that the FDA did not abuse its discretion in finding the color not within the scope of Delaney, citing *Monsanto*.<sup>178</sup> There was also found to be no reasonable risk of harm caused by the presence of p-toluidine in the color.<sup>179</sup>

One technical aspect that the FDA has narrowly avoided in litigation in applying the Delaney is the concept of the "appropriateness" of the test to measure a chemical's ability to induce cancer. The text of the clause specifically mandates carcinogenic evidence as derived from animal experiments or incidence in man.<sup>180</sup> The FDA has avoided the issues of how much and what sort of animal tests are required. Some documentation has been present from the inception of the clause and has been reinforced by FDA publications.<sup>181</sup> One test that has never been held adequate is mutagenicity data, derived from *in vitro* assays which are specifically sensitive to detect

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<sup>173</sup>Hearings on Food Safety Before the Committee on Labor and Human Resources, 98th Cong. 1st Sess. (June 8-10, 1983).

<sup>174</sup>The Food Safety Hearings stimulated a flurry of bills all designed to modify the Delaney Clause. See Silverglade, *The Risks of Risk Assessment and Risk-Benefit Analysis*, 38 FOOD DRUG COSM. L.J. 318 (1983) (giving a summary and evaluation of bills submitted in 1983). See also S. Rep. No. 1938, 98th Cong. 1st Sess., 129 CONG. REC. 13778 (1983) (bill following the *de minimis* approach).

<sup>175</sup>728 F.2d 322 (6th Cir. 1984).

<sup>176</sup>FD&C Green No. 5 has p-toluidine as an unavoidable impurity, thus compound has been found to be carcinogenic. *Id.* at 323.

<sup>177</sup>The court seemed to follow the "constituents approach" as set forth by the FDA regulations. *Id.* at 325. See generally 47 Fed. Reg. 14,464 (1982).

<sup>178</sup>728 F.2d at 325 (6th Cir. 1984).

<sup>179</sup>*Id.*

<sup>180</sup>Delaney requires that the compound will not be found safe "if it is found, after the appropriate tests" to induce cancer in man or animals. 21 U.S.C. §§ 348, 360b, 376 (1970).

<sup>181</sup>Current testing criteria are outlined in U.S. FDA, TOXICOLOGICAL PRINCIPLES FOR THE SAFETY ASSESSMENT OF DIRECT FOOD ADDITIVES AND COLOR ADDITIVES USED IN FOOD (1982) [Hereinafter Redbook] This publication contains extensive sections on assessment of safety, guidelines for toxicological tests, adequacy of tests and decision-making.

alteration in DNA.<sup>182</sup> Despite its sensitivity, the test has the tendency to elicit false negatives or false positives as determined by follow-up animal studies.<sup>183</sup> In terms of a carcinogenic model, it is thus best left for screening purposes.<sup>184</sup>

What may be gleaned from this discussion of the legislative history and judicial interpretation of the Delaney Clause is that the clause is seldom used. The FDA frequently opts to use the General Safety Clause, and even when Delaney is used there is a tendency to avoid full application. From the beginning, the FDA's attempt to implement Delaney can be described as a futile attempt to place a strict regulation on a subject matter that is in continuous metamorphosis.

The technical short-comings of the Delaney Amendment are the principle reason for its falling into disfavor at the present time. While an excellent statement of public policy,<sup>185</sup> it completely fails as a regulation designed to facilitate control of biological processes. To evaluate the applicability of future changes to the Delaney Clause and to make rational decisions based on that evaluation requires a clearer understanding of the cancer process.

### III. Principles and Evaluation of Carcinogenesis

The reason the Delaney Clause has been such a difficult law to implement stems from the subject matter to which it relates. The cancer process is a multistage and multi-factorial event. If one considers biological homeostasis in continuum, the induction of cancer may take place at one instant, but

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<sup>182</sup>*Infra* note 230 and accompanying text (mutagenicity and the Ames test).

<sup>183</sup>False negatives involve data derived from animal studies where the dose of the compound was inadequate, the study did not last long enough or the species was resistant. False positives usually are presented by doses (given that are physiologically not tolerated), the increased incidence of spontaneous tumors, or chemical impurities. *Infra* note 201-206 and accompanying text (mechanisms of carcinogenicity). See also Oser, *An Assessment of the Delaney Clause After 15 Years*, 29 FOOD DRUG COSM. L.J. 201, 207 (1974).

<sup>184</sup>Principles, *supra* note 5, at 10, 424; See Editorial, "Delaney Amendment" 1 PREVENTATIVE MEDICINE 292 (1972); Stokinger, *Sanity in Research and Evaluation of Environmental Health*, 174 SCIENCE 662 (1971) (discussions on "appropriateness" of tests).

<sup>185</sup>See Hutt, *Public Policy Issues in Regulating Carcinogens in Food*, 33 FOOD DRUG COSM. L.J. 541 (1978). The author points out that the Delaney Clause was never meant to be a statement of scientific truth but rather announcement of public policy. This may be entirely correct but in the regulation of such things as carcinogens the scientific rationale cannot be secondary consideration without encountering serious problems in implementation.



there is usually no response until some later time.<sup>186</sup> Manifestation of the carcinogenic response results from and is affected by a variety of biologic factors.

In 1982, FDA published toxicological principles for the safety assessment of food additives<sup>187</sup> and in 1985 the Office of Science and Technology Policy set forth a review of chemical carcinogenesis;<sup>188</sup> these documents provided in-depth analysis of this rather complex process. The focus of this section is to present the material required to understand the procedures and goals of regulating carcinogens in food. Also presented will be a review of current risk assessment methods which provide a more realistic approach to regulating food additives and carcinogens.

### A. Cancer Process and the Delaney Clause

In the 15th Century, Paracelsus noted, "All things are poisonous, for there is nothing without poisonous qualities. It is only the dose which makes a thing a poison." (Paracelsus, 1493-1541).<sup>189</sup> This quote highlights the most important concept in the regulation of toxins and carcinogens, namely that everything may be poisonous and may have the potential to cause cancer, including compounds essential to human life.<sup>190</sup> The FDA's regulation of additives and animal drugs purports to cover only a small portion of the wide spectrum of chemicals to which man is exposed; the Delaney Clause narrows this range even further by focusing on substances ingested by man or animals.<sup>191</sup>

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<sup>186</sup>Homeostasis may be described as the stability of an organism to maintain bodily functions in a maximal and controlled manner. In relation to cancer, an agent may cause a lesion that is repaired by the organism or due to homeostatic mechanisms does not present itself until a much later time. See generally DORLAND'S POCKET MEDICAL DICTIONARY 328 (23d ed. 1982). For a general discussion of these principles, see CASARETT & DOULL, *supra* note 5, at 84-138 (chemical carcinogens); PRINCIPLES OF DRUG ACTION, *supra* note 24 at 667-702.

<sup>187</sup>Evaluating Assays, *supra* note 48.

<sup>188</sup>See *supra* note 181.

<sup>189</sup>CASARETT & DOULL, *supra* note 5, at title page. (Paracelsus, 1493-1541)

<sup>190</sup>Proteins and minerals such as tryptophan, selenium, calcium as well as endogenous hormones all may cause cancer if ingested at the appropriate dose. See generally *Article of Faith*, *supra* note 31, at 589; Martin, *The Delaney Clause and Zero Risk Tolerance*, 34 FOOD DRUG COSM. L.J. 43 (1979).

<sup>191</sup>The FDA has jurisdiction to regulate all foods, drugs, cosmetics and medical devices. This subject matter covers all possible routes of exposure i.e. not only ingestion but dermal applications, etc. See 21 U.S.C. §§ 348, 360b, and 376 (1970). See also 21 U.S.C. § 331 (1970) (prohibiting the introduction into interstate commerce of adulterated foods, drugs, devices or cosmetics).

Since its inception this clause has been the subject of scientific attack, mainly because it ignores a basic tenet in pharmacology/toxicology; it refuses to account for any dose-response relationship.<sup>192</sup> This relationship was contemplated by the drafters but due to the overwhelming fear of the cancer of the time, Congress deemed it necessary to ban all carcinogens.<sup>193</sup> Assuming the Delaney Committee's premise that it was impossible to determine a threshold dose (which in some instances does seem to be supported by evidence), the Amendment's coverage was drafted too narrowly by only covering food additives, and not pesticides or natural constituents.<sup>194</sup> Congress also carved two broad exceptions: substances listed as GRAS and Prior-Sanctioned Ingredients.<sup>195</sup> In terms of total risk, then, the Delaney Clause eliminated very little. Perhaps the best thing that may be said is that the Amendment fostered the public awareness that all things put into the environment and our food tend to return. Historically, this public awareness began to appear shortly after Rachel Carson published *Silent Spring*<sup>196</sup>

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<sup>192</sup>The Delaney Clause precludes any food additive from being found safe if it has been found to induce cancer in man or animals. This ban does not consider any dose element. This concept is known as the "one-hit" theory where one molecule of the carcinogenic substance causes irreparable damage regardless of dose. While this may be true, current research has shown that some carcinogens do act in a dose-related manner. Figure 1 below illustrates this type of mechanism.

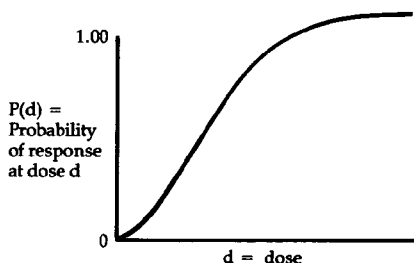


Fig 1. — A dose-response curve.

The abscissa represents dose and the ordinate the probability of response at the given dose. From such studies dose relate carcinogenesis may be shown. Van Ryzin, *Quantitative Risk Assessment*, 22 J. OCCUPATIONAL MED. 321, 322-23 (1981); *infra* note 202 and accompanying text (genetic and epigenetic carcinogens).

<sup>193</sup>The "one-hit" theory of carcinogenesis is still a viable theory today, but in the 1950's there were few other alternatives. At the time determination of safe levels of carcinogens was for the most part impossible. See *Article of Faith*, *supra* note 31 and accompanying text, for current risk assessment models showing how such determinations may be made. *Infra* note 201 and accompanying text.

<sup>194</sup>See *supra* text accompanying notes 3 and 58.

<sup>195</sup>See *supra* notes 51-52 and accompanying text.

<sup>196</sup>R. CARSON, *SILENT SPRING* (1962). This book drew attention to the interaction of chemicals

and was also evident at the Delaney hearings.<sup>197</sup> Everything from the steaks we barbecue to the bread we bake may contain cancer-causing agents, provided we are exposed to a high enough level or wait a long enough time.<sup>198</sup> In fact, prolonged physical irritation has been shown to induce cancer. This is the purported mechanism behind the mesotheliomas caused by asbestos.<sup>199</sup>

The Delaney Committee's refusal to find a cancer threshold was based on the concept known as the "one-hit" theory.<sup>200</sup> Briefly, this theory states that to induce carcinogenesis, all that is required is exposure to one molecule.<sup>201</sup> The "one-hit" theory has never been disproved but it must be qualified. First, by using this theory one is referring to a specific type of carcinogenic mechanism, *i.e.*, genetic or direct carcinogens.<sup>202</sup> For such a significant event

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with biological systems and set forth the notion that once something is put into the environment it is not gone forever.

<sup>197</sup>The Delaney Hearings may be characterized as a way to halt the indiscriminate use of hazardous chemicals in the nations food supply. See *Delaney Proviso*, *supra* note 26, at 557 (describing the tenor of the Delaney proceedings).

<sup>198</sup>The grilling of animal tissue or the burning of any organic matter forms releases benzo(A)pyrene, a potent animal carcinogen. See CASARETT & DOULL, *supra* note 5, at 92. Wheat is usually contaminated with some level of aflatoxins, which are a group of toxins produced from the mold *Aspergillus flavus*. Aflatoxin B<sub>1</sub> is known to be a potent hepatotoxin and its presence in wheat is practically unavoidable. This compound is regulated by the FDA under the General Safety Clause (§ 401(a)) and wheat is found to be unsafe at 15 ppb. It should be noted that the low levels appear to be innocuous, because liver cancer is a relatively rare disease. See AMERICAN CANCER SOCIETY, 1979 FACTS AND FIGURES (1978); 39 Fed. Reg. 42,748 (1974). These examples are provided to illustrate that in the right dosage range practically anything may cause cancer. This extreme position that must be qualified. The onset of toxic effects in many cases often preclude the occurrence of a carcinogenic event, thus one may be poisoned before bioaccumulating a dose high enough to cause cancer. Carcinogens that deserve scrutiny and regulation usually work by a particular (direct) molecular mechanism. *Infra* notes 201-206 and accompanying text. See generally, CASARETT & DOULL, *supra* note 5, at 93. But see *supra* note 193.

<sup>199</sup>This concept is known as the "Physical Carcinogen Theory" where the elicitation of an inflammatory response may induce tumor formation and growth. It is by this mechanism that carcinogens that do not react with DNA or interfere with a more classic physiological pathway probably work. See *Chemical Carcinogens*, *supra* note 5, at 10,386. This is the purported cause of mesotheliomas arising from asbestos exposure. Kammerstein and Churg, *Pathology of Carcinoma of the Lung Associated with Asbestos Exposure*, 30 *CANCER* 14 (1972).

<sup>200</sup>The term "threshold" is used synonymously with "no effect level", and means the level at which experiments indicate no increased incidence of tumors over background. See DORLAND'S POCKET MEDICAL DICTIONARY 679 (23rd ed. 1982).

<sup>201</sup>This theory assumes that each molecule of a substance that enters the organism is free to interact with DNA or some other functional macromolecule and induce cancer. See Mantel and Schneiderman, *Estimating "Safe Levels, A Hazardous Undertaking*, 35 *CANCER RES.* 1379, 1382 (1975).

to take place, a chemical/DNA interaction must occur.<sup>203</sup> These carcinogens tend to be highly mutagenic and thus detectable in short-term or *in vitro* assays.<sup>204</sup> Indirect or epigenetic carcinogens do not have a direct DNA component; instead exposure to these substances causes pathologic changes that facilitate or promote tumor growth by another mechanism.<sup>205</sup> This latter mechanism does allow for a dose-response relationship.<sup>206</sup>

Often when reading regulatory data one will come across the terms initiator and promoter. Initiators sometimes are mistakenly referred to as genetic carcinogens (described above) but are more correctly defined as agents responsible for the induction of irreversible alterations in genetic material.<sup>207</sup> It is important to emphasize that just because this event has taken place, one is not necessarily destined to contract cancer. This may or may not be a one-shot phenomena, and the process may also depend on dose or co-exposure to other substances.<sup>208</sup> Initiation is merely one stage of this process, one

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(procarcinogen) is metabolized into a biologically active agent. Other direct mechanisms may include viral transformation of oncogenes. Epigenetic carcinogens (indirect) utilize some secondary mechanism, such as blockade of a metabolic detoxification pathway. These have the tendency of causing cancer in a dose dependant manner, i.e., the higher the dose the increase in incidence of tumors, and are reversible. See generally *Chemical Carcinogens*, *supra* note 5.

<sup>203</sup>In order for the one-hit theory to work the chemical must directly interact with the target tissue of the animal i.e. a direct or genetic (DNA) mechanism. This is because the one-hit theory does not lend itself to a dose-response relationship, e.g. theoretically the animal would contract cancer on the first hit and recovery would be precluded thereafter. It should be noted that a distinction is being made between incidence of cancer and incidence of tumors. Under the one-hit scheme the incidence of tumors would be dose-dependent, i.e., each molecule that enters induces one new tumor. This rationale like the cancer process it describes is not foolproof. Many argue that the one-hit theory is the predominant mechanism because incidence of cancer is dependent on tumor latency (time from DNA alteration to presentation of cancer) and thus with each new hit the latency is shortened. See generally *Chemical Carcinogens*, *supra* note 5, at 10,390 (Cancer formation section).

<sup>204</sup>"Mutagen" refers to a chemical capable of altering DNA structure. DORLAND'S POCKET MEDICAL DICTIONARY 430 (23rd ed. 1982). The cancer process is thought to be initiated by an alteration in DNA, which then causes uncontrolled cellular proliferation. See CASARETT & DOULL, *supra* note 5, at 85-130 (Chemical Carcinogens).

*In vitro* assays are short term bacterial assays which are capable of measuring a compound's mutagenic potential. See Ames, McCann and Yamaski, *Methods for Detecting Carcinogens and Mutagens with the Salmonella Mammalian Microsome Mutagenicity Test*, 31 MUTATION RES. 347 (1975).

<sup>205</sup>See *supra* note 202.

<sup>206</sup>*Id.*

<sup>207</sup>Initiators may be likened to primary or direct carcinogens, the presence of which is required for tumor induction. *Chemical Carcinogens*, *supra* note 5, at 10,390.

<sup>208</sup>DNA repair mechanism, metabolic pathways and a species' biologic characteristics may cause profound variation as to the way a carcinogen will react and the effect that it will have. *Id.* at 10,387. See also note 211 and accompanying text (Promoters).

which may remain latent for years.<sup>209</sup> But as the number of "initiators" increases (dose or agent) so do the chances that the process will proceed to the next stage.<sup>210</sup> Promoters, on the other hand, do not necessarily cause this sort of interaction and may be distinguished from epigenetic agents because they usually do not cause a pathologic change that leads to a direct carcinogenic event. These substances may act to saturate the detoxification pathways (or excretion routes) of initiators, inhibit DNA repair mechanisms or promote cell proliferation by a hormonal mechanisms.<sup>211</sup> Figure 2 illustrates this process, (see page 201 text).

Carcinogenic potency is an elusive term to define and is based on a variety of factors. In simple terms, it refers to a substance's ability to penetrate the organism and reach a target site at a concentration sufficient for that compound to cause a carcinogenic event.<sup>212</sup> Relevant factors vary from agent to agent but depend upon the chemical nature of the compound, route of exposure, metabolism, pharmacokinetics and target tissue.<sup>213</sup> Figure 2 illustrates this process:

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<sup>209</sup>Latency or "time-to-tumor" refers to a process called neoplastic progression whereby cellular alteration leads to tumor formation. This state of cellular transition from DNA damage to tumor formation is often termed "somatic mutation". See *infra* note 213 and accompanying text. The time required for this progression may take years. See generally *Chemical Carcinogens*, *supra* note 5, at 10,393.

<sup>210</sup>See *Chemical Carcinogens*, *supra* note 5, at 10,392.

<sup>211</sup>These mechanisms are collectively categorized as host defense mechanisms and may repair or mitigate the chemical insult. Depending on the organism, the chemical, or the dose, these mechanisms may either stimulate or inhibit carcinogenic insult. *Id.*

<sup>212</sup>Fundamental to this concept is the idea that most carcinogens have a specific target tissue i.e. a tissue at which tumor induction first occurs. This increased propensity for tumors at one given site over another may be due to the molecular structure of the compound, a unique aspect of the tissue, the biological activity of the tissue (presence of metabolic pathways, lack of DNA repair, or receptor sites) or a combination of these effects. One example of this tissue specificity is seen with aflatoxin, as previously discussed in note 197. See *PRINCIPLES OF DRUG ACTION*, *supra* note 24, at 667-68.

<sup>213</sup>The chemical nature of the agent may predetermine its carcinogenic potential. Polycyclic aromatic hydrocarbons such as Benzo(A)pyrene (found in grilled foods) is a chemical with a structure which identifies it as a carcinogen. The route of exposure may determine if and where a carcinogen will act. The Delaney clause only deals with ingested foods, but carcinogenic risk from drugs, foods and cosmetics may be from a number of routes, i.e. inhalation, dermal application and intravenous. Metabolism also plays an important role in the carcinogenesis of a compound. From a regulatory point of view, it must be realized that exposure to multiple agents may alter how one or more of the agents will react by the way the body activates or deactivates the compound. See Miller, *Some Current Perspectives on Chemical Carcinogenesis in Humans and Experimental Animals: Presidential Address*, 38 *CANCER RESEARCH* 1479 (1978) (structure of chemical carcinogens, metabolism of foreign compounds). See generally CASARETT & DOULL, *supra* note 5, at 667-702; *infra* note 291 and accompanying text (Pharmacokinetics).

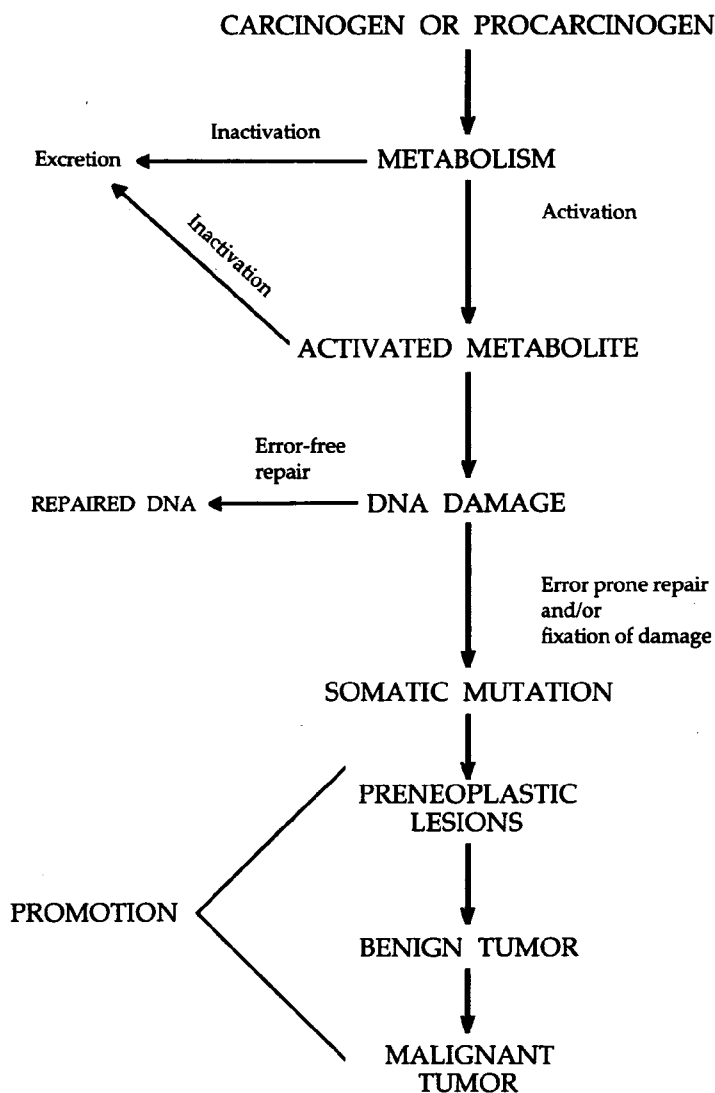


FIGURE 2. SIMPLIFIED VIEW OF BIOLOGICAL EVENTS INVOLVED IN CHEMICAL CARCINOGENESIS<sup>214</sup>

<sup>214</sup>Bull, *Experimental Methods for Evaluating the Health Risks Associated with Organic Chemicals in Drinking Water*, 6 TOXIC AND ENVIR. CHEM. 1 (1982).

It should be noted that no distinction should be made between benign and malignant tumors in the regulation of carcinogens.<sup>215</sup> A benign tumor may be thought of as a site which has undergone uncontrolled cell proliferation and for some reason has ceased; whether or not the lesion actually becomes malignant is unimportant because there has clearly been a cellular change.<sup>216</sup> The prognosis, however, is most often radically different.

The Delaney Clause in present form fails to make any of these biological distinctions. As an illustration, cyclamates and saccharin were in use prior to 1958 and were GRAS-listed following the enactment of the Food Additives Bill.<sup>217</sup> Cyclamates were eventually found to be carcinogenic and banned.<sup>218</sup> Despite questionable data and further tests tending to show that it was a promoter rather than primary carcinogen (initiator), saccharin was proposed to be banned under Delaney in 1977.<sup>219</sup> Saccharin was shown to increase incidence of bladder tumors when it was given in combination with cyclamates.<sup>220</sup> The public outcry which followed was unprecedented. Saccharin was not only a favorite of weight-conscious Americans, but was useful in controlling such conditions as obesity and hyperglycemia.<sup>221</sup> The FDA's own press release did little to help the credibility of the data, since it stated that there was no evidence linking it to cancer in humans. This led Congress to place an 18 month moratorium on the ban.<sup>222</sup> While comprehensive data has yet to come in, some evidence indicates saccharin is not the carcinogen it was originally purported to be.<sup>223</sup> Statistical misinterpretation has also been implicated in the banning of C & D Red No. 2 under the General Safety Clause.<sup>224</sup>

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<sup>215</sup>See Food and Drug Administration Advisory Committee on Protocols for Safety Evaluation: Panel on Carcinogenesis Report on Cancer Testing in the Safety Evaluation of Food Additives and Pesticides, 20 TOXICOL. APPL. PHARM. 419 (1971).

<sup>216</sup>See Problems in the Evaluation of Carcinogenic Hazard From Use of Food Additives, (Sub-Committee on Carcinogenesis, Food Protection Committee and Food Research Council, NAS-NRC) 21 CANCER RES. 429, 432 (1961) (benign versus malignant tumors). [Hereinafter Food Protection Committee.]

<sup>217</sup>24 Fed. Reg. 9,368 (1959) (GRAS listings).

<sup>218</sup>45 Fed. Reg. 61,474 (1980) (Banning of Cyclamates).

<sup>219</sup>42 Fed. Reg. 19,996 (1977) (Proposed Rules on Saccharin).

<sup>220</sup>*Supra* note 218.

<sup>221</sup>Saccharin Ban and Food Safety Policy: Hearings before the Sub-Committee on Health and Scientific Research of the Senate Committee on Labor and Human Resources, 96th Cong., 1st Sess. 231 (1979).

<sup>222</sup>See generally Schultz, *The Bitter Aftertaste of Saccharin*, 40 FOOD DRUG COSM. L.J. 66, 72 (1985).

<sup>223</sup>Saccharin has been purported to be a promoter rather than direct carcinogen. See CASARETT & DOULL, *supra* note 5, at 116 See also Friedel, *National Bladder Conference*, 37 CANCER RES. 734 (1977).

<sup>224</sup>Kirschman, *Toxicology - The Exact Use of an Inexact Science*, 31 FOOD DRUG COSM. L.J. 455 (1976).

### B. Evaluation of Data and Setting Tolerances Based on Carcinogenic Risk

A comparison on Delaney Clause interpretation and current knowledge of carcinogenesis leads to the conclusion that regulation under this standard is unworkable. The question then follows what standard should be used to protect the public from these hazardous substances? The possibility exists that there may never be a straight-forward standard that will allow regulation of all carcinogens. This is not based on a lack of knowledge alone, but rather upon the complexities and diversities of the cancer process itself.

Current knowledge suggests that regulation of carcinogens should resemble that of compounds regulated by the General Safety Clause, though utilizing a more conservative approach primarily focusing upon risk.<sup>225</sup> Risk is a relative term that requires scientific as well as moral judgments to be made.<sup>226</sup> Because it resists relative risk judgment, the Delaney Clause has been the focal point of much criticism.<sup>227</sup> Scientific judgments guided by public policy considerations are not difficult to perform, and if correct procedures are set forth, they may in fact become routine.

Quantitative risk assessment procedures may allow for these judgments.<sup>228</sup> Specifically one should consider the compound<sup>229</sup> and its uses.<sup>230</sup> If, for example, an additive or any substance subject to regulation performs no useful purpose and preliminary data tends to show that it is a potent carcino-

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<sup>225</sup>This proposal deals with the sort of risk-benefit analysis found in the General Safety Clause, but is modified to account for the biological mechanisms of cancer. See 21 U.S.C. § 342 (as amended 1970). Carcinogens by nature require more strict scrutiny and assurance that the risk of harm is minimal; this requires a greater margin of safety to be used in the calculation of safe levels. *Infra* note 275 and accompanying text (margin of safety).

<sup>226</sup>See Hutt, *Public Policy Issues in Regulating Carcinogens in Food*, 33 FOOD DRUG COSM. L.J. 541 (1978).

<sup>227</sup>See Matson, *Scientific Judgment in Law and Regulation*, 15 FOOD DRUG COSM. L.J. 70 (1960); Coon, *The Delaney Clause*, 2 PREVENTATIVE MEDICINE 150 (1973).

<sup>228</sup>See generally Interdisciplinary Panel on Carcinogenicity, *Criteria for Evidence of Chemical Carcinogenicity*, 225 SCIENCE 682 (1984); *Quantitative Risk Assessment*, 18 FOOD COSM. TOXICOLOGY 711 (1980). [Hereinafter *Quantitative Risk Assessment*].

<sup>229</sup>*Supra* note 213 and accompanying text (evaluation of chemical structure).

<sup>230</sup>Use analysis not only includes the extent and manner in which a compound is used in evaluating food, or the prevalence of the compound in a given foodstuff, but also an estimation of the population at risk, i.e. conditions of exposure, number of persons affected and age of those affected. *Quantitative Risk Assessment*, *supra* note 228.



gen (e.g., in the range of  $10^{-3}$ )<sup>231</sup> zero tolerance may be a rational alternative.<sup>232</sup> At this point technological and economic feasibility may also be considered. However, since this is a public health problem, present technology-forcing measures should not be ruled out.<sup>233</sup> Once it has been shown that a carcinogen is worthy of regulation, one may then proceed to predict "a safe" level.<sup>234</sup>

Quantitative risk assessment evaluates chemicals and other agents on a case-by-case basis using mathematical models.<sup>235</sup> These mathematical models utilize data points from observed exposure levels to formulate dose-response-type curves which may then be used to predict risk at lower exposures.<sup>236</sup> The use of a particular model or curve can be justified by the "mathematical" fit to the available data points.<sup>237</sup> The use of these types of procedures is based upon the understanding that the mathematical curves are reflective of the biological factors that are present when an organism is exposed to a carcinogen.<sup>238</sup>

[The] biological factors which may play important roles in the risk assessment are (1) dose of the material at the sensitive tissue; (2) the sensitive tissue(s) itself; (3) the nature of the response(s); (4) rates

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<sup>231</sup>Generally speaking a negative exponent is used to denote "one in a . . ." chance of contracting cancer e.g.  $10^{-3}$  - one in a thousand. This risk is considered by most to be quite high, the benchmark seem to be  $10^{-6}$  (one in a million) as proposed by Mantel and Bryan in 1961. A life-time risk at this level would roughly correspond to three additional cancer deaths in the U.S. per year. *Id.* at 713. See Mantel and Bryan, "Safety" Testing of Carcinogenic Agents, 27 J. NAT'L CANCER INST. 455 (1961).

<sup>232</sup>Thus the rationale of the Delaney Amendment may in fact be applicable in those rare instances where the chemical is a potent carcinogen (genetic) with little or no beneficial use and with the potential to expose a great number of people. See generally Kennedy, *Priority Setting in the Real World*, 32 FOOD DRUG COSM. L.J. 527, 531 (1977).

<sup>233</sup>This concept has been previously used in the setting of safe levels of "added" substances. See *Monsanto*, 613 F.2d at 954. (If the Commissioner, in his review estimated an acceptable acrylonitrile level he could issue a statement prescribing it. It would then be up to the industry to meet an acceptable level).

<sup>234</sup>These levels may be predicted on the basis of Virtually Safe Doses (VSD's). *Infra* note 258 and accompanying text.

<sup>235</sup>Quantitative risk assessment is not to be restricted solely to chemicals, it is currently being used to evaluate chemicals, biologicals, viral particles and radiation levels, all of which may induce cancer and could be found in food. Principles, *supra* note 5, at 10,383-19,387. Because the mechanisms of cancer may vary, case-by-case evaluation of separate (or related) compounds is necessary. See Interdisciplinary Panel on Carcinogenicity, *Criteria for Evidence of Chemical Carcinogenicity*, 225 SCIENCE 682, 683 (1984). [Hereinafter *Criteria for Chemical Carcinogenicity*].

<sup>236</sup>See generally *Quantitative Risk Assessment*, *supra* note 228.

<sup>237</sup>See Krewski and Van Ryzin, *Dose Response Models for Quantal Response Toxicity Data*, in: CURRENT BOOK TOPICS IN PROBABILITY AND STATISTICS (1981) [hereinafter Krewski and Van Ryzin]; Van Ryzin, *Quantitative Risk Assessment*, 22 J. OCCUPATIONAL MED. 321 (1980).

<sup>238</sup>Occupational Exposure to Ethylene Dibromide, 48 Fed. Reg. 45,956, 45,969 (1983).

and sites of biotransformation; (5) toxicity of metabolites; (6) chronicity of the compound (cumulative nature of the material or its actions); (7) pharmacokinetic distribution; (8) the effect of biological variables such as age, sex, species and strain of test animals; (9) and the manner and method of dosing the test animals.<sup>239</sup>

While it may be impossible to fit all of these factors into one model, comparisons of different data sets within the various risk assessment procedures should be made.<sup>240</sup>

Risk assessment procedures consider data from four sources: chemical assays, short-term toxicity tests, chronic animal studies, and epidemiologic tests.<sup>241</sup> They follow the general scheme of hazard identification (qualitative data indicative of carcinogenic activity) exposure assessment (population at risk at various levels and duration of doses), and mathematical modeling.<sup>242</sup> These procedures attempt to translate biological activity into safe dose levels based on data derived from animals and/or previous human exposure.<sup>243</sup>

The criteria for animal studies that may be used for risk assessment is strictly a matter of scientific judgment.<sup>244</sup> The function and validity of such tests are impacted by a number of considerations. First, positive results are found in long-term (chronic) animal studies when administration of the agent, in adequately designed and conducted experiments, demonstrates an increased incidence of one or more types of tumors in treated animals as compared to untreated animals maintained under identical conditions.<sup>245</sup> Further changes in tumor latency<sup>246</sup> and numbers of tumors<sup>247</sup> also tend to be indicators of carcinogenic potency.<sup>248</sup> Testing should be done under experi-

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<sup>239</sup>*Id.*

<sup>240</sup>*Id.*; Silverglade, *The Risk of Risk Assessment and Risk-Benefit Analysis*, 38 FOOD DRUG COSM. L.J. 318, 319 (1983).

<sup>241</sup>See Principles, *supra* note 5, at 10,424.

<sup>242</sup>*Id.*

<sup>243</sup>These methods are used to translate biological activity into safe doses by using mathematical models which assign numerical values to the various parameters involved in the toxic or carcinogenic response. See Van Ryzin, *Quantitative Risk Assessment*, 22 J. OCCUPATIONAL MED. 321, 322 (1980) (illustration of models).

<sup>244</sup>*Article of Faith*, *supra* note 31, at 589. *supra* note 181. See Redbook. The Redbook contains guidelines and explanations of methods that should be used in the execution of appropriate toxicological tests. It includes such methods as design of pilot studies, selection of dose, and methods of tumor evaluation. See also 21 C.F.R. Pt. 58 (1985) (FDA Good Laboratory Practices which standardize research and data collection techniques).

<sup>245</sup>*Criteria for Chemical Carcinogenicity*, *supra* note 235, at 683.

<sup>246</sup>*Supra* note 209 and accompanying text.

<sup>247</sup>*Criteria for Chemical Carcinogenicity*, *supra* note 235, at 683.

<sup>248</sup>Food Protection Committee, *supra* note 216, at 432 (potent and weak carcinogens).

mental conditions likely to yield maximal tumor incidence.<sup>249</sup> Both the scientist and regulator should be aware that other conditions such as stress and irritation may themselves induce tumor formation.<sup>250</sup>

Epidemiologic studies, when available, are the only reasonable means of directly assessing the carcinogenic potential of agents in humans. Studies are limited by availability and relevance, as well as lack of scientific validation of results.<sup>251</sup> Such studies can be separated into two categories: descriptive (hypothesis generating) and analytical (hypothesis testing).<sup>252</sup> The descriptive studies explore the relationship between exposure and tumor development at specific target sites.<sup>253</sup>

Analytical studies are designed to test hypothesized relationships and may be further differentiated into case comparison and cohort studies.<sup>254</sup> Case studies compare past histories of exposure and personal characteristics of cancer patients with those from similar settings who do not have cancer.<sup>255</sup> Cohort studies examine the personal histories and characteristics of a sample population through time and determine a rate of cancer within that population.<sup>256</sup>

Once data has been collected from the various studies of risk, assessment based on dose-response-type curves may be conducted.<sup>257</sup> The goal of such a

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<sup>249</sup>See generally Nat'l. Toxicology Program Ad Hoc Panel on Chemical Carcinogenesis Testing and Evaluation (1984) (defining "Maximal Tolerated Dose" (MTD) as the amount of agent needed to elicit a response without significantly altering the animal's life span).

<sup>250</sup>*Id.* See also Principles, *supra* note 5, at 10,413; *supra* note 199 and accompanying text (physical carcinogens).

<sup>251</sup>Principles, *supra* note 5, at 10,420 (limitations of epidemiology).

<sup>252</sup>See generally *Criteria for Chemical Carcinogenicity*, *supra* note 235, at 682-683 (types of epidemiology studies).

<sup>253</sup>Scientific Bases for Identification of Potential Carcinogens and Estimation of Risks, 44 Fed. Reg. 39,858 (1979).

<sup>254</sup>*Id.*

<sup>255</sup>See generally, Principles, *supra* note 5, at 10,422.

<sup>256</sup>*Id.* Each of these studies evaluate different parameters, i.e. case studies examine cancer patients in a finite patient population, whereas cohort studies examine a particular population through time. One should be aware that case studies require a control group (non-exposed group) while cohort studies require that the exposed group is complete as possible (to detect all cases possible). See Muir, *Limitations and Advantages of Epidemiological Investigations of Environmental Carcinogenesis*, 329 N.Y. ACAD. OF SCIENCES ANNALS 152 (1979). To one evaluating this data it is important to ensure that the previously described classification(s) have been made because misuse of data will lead to erroneous risk determinations. This hazard may only be determined from extrapolation from higher dosages. Epidemiology studies may, however, indicate the limit within which a specific type of exposure will affect the incidence of cancer in humans. *Criteria for Chemical Carcinogenicity*, *supra* note 234, at 683.

<sup>257</sup>*Supra* note 192 (illustration of Dose-Response Curve, Figure 1).

procedure is to estimate a Virtually Safe Dose (VSD), which corresponds to a predetermined low level of increased risk over a spontaneous background rate.<sup>258</sup> No one model is preferred; in fact, a variety should be tested to determine the best mathematical fit for high dose to low dose extrapolation.<sup>259</sup> This method may even permit the application of the One-Hit Theory of carcinogenesis.<sup>260</sup>

These mathematical models fall into two broad groups: tolerance distribution and mechanistic models.<sup>261</sup> Tolerance (threshold) models are based on the premise that each individual in the population has a tolerance dose to the test compound after which a response is seen (e.g., increased incidence of cancer).<sup>262</sup> Mechanistic or stochastic models are based on biological principles which lead to an expression of the probability of a response at any given dose.<sup>263</sup> Due to the nature of the cancer process, the latter appears to be more applicable, although threshold modeling is less complex, hence easier to perform.<sup>264</sup>

The Mantel-Bryan Method<sup>265</sup> currently employed by the FDA is technically a tolerance model, but is rather unique.<sup>266</sup> Instead of curve fitting, it uses a data curve which intentionally lies above the actual dose response curve.<sup>267</sup>

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<sup>258</sup>Crump, Guess and Deal, *Confidence Intervals and Tests of Hypotheses Concerning Dose Response Relations Inferred From Animal Carcinogenicity Data*, 33 *BIOMETRICS* 437 (1977) (determinations of VSD's).

Risk levels may range from  $10^{-4}$  to  $10^{-8}$ . Cornfield, Carlborg and Van Ryzin, *Setting Tolerances on the Basis of Mathematical Treatment of Dose-Response Data Extrapolated to Low Doses*, in *PROCEEDINGS OF THE FIRST INT'L. CONGRESS ON TOXICOLOGY* 143 (1978) (level of risk values) [Hereinafter *Setting Tolerances*]; *infra* note 270 (Mantel-Bryan Method, Figure 3).

<sup>259</sup>See Occupational Exposure to Ethylene Dibromide, 48 Fed. Reg. 45,956, 45,969-970. "Mathematical fit" is a term used to describe how well the data correlates to the dose-response curve. Extrapolation is the prediction of risk outside the range of the observed data. Interpolation is the prediction of risk within the range of the observed data.

<sup>260</sup>*Supra* note 192 (One-Hit Theory of Carcinogenesis).

<sup>261</sup>Chand and Hoel, *A Comparison of Models for Determining Safe Levels of Environmental Agents*, in *RELIABILITY AND BIOMETRY; STATISTICAL ANALYSIS OF LIFELONGTH* 381 (1974).

<sup>262</sup>*Id.*

<sup>263</sup>See Krewski and Van Ryzin, *supra* note 237, at 201.

<sup>264</sup>This is because a less rigorous review is required. See *Evaluating Assays*, *supra* note 48 at 17,087-17,088 (explanation of Mantel-Bryan Method).

<sup>265</sup>Mantel, Bodihar, Brown, Ciminera and Tukey, *An Improved Mantel-Bryan Procedure for "Safety" Testing of Carcinogens*, 35 *CANCER RESEARCH* 865 (1975). [Hereinafter *Improved Mantel-Bryan Procedure*].

<sup>266</sup>See Peto, Lee and Paige, *Statistical Analysis of the Bioassay of Continuous Carcinogens*, 26 *BR. J. CANCER* 258 (1972) (discussion of Probit (tolerance) Models).

<sup>267</sup>This concept is known as "Conservativeness" of procedure where the dose allowed is lower than the actual VSD. See *Setting Tolerances*, *supra* note 258, at 143.

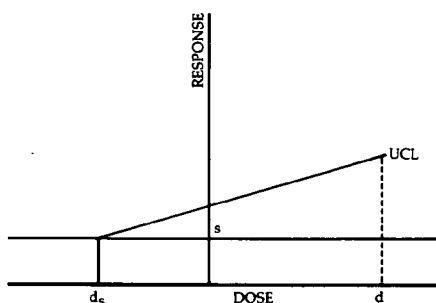
It also has been modified to account for tumor latency.<sup>268</sup> This method requires the setting of a maximally permissible risk and the "appropriate" studies<sup>269</sup> be performed with a dose-response curve drawn from the data.<sup>270</sup> The pre-setting of a maximum permissible level (usually  $10^{-6}$ ) is a way of providing a margin of safety for all compounds and thus distinguishes the method from those which set specific thresholds for each compound. Because it uses confidence limits of 95 to 99 percent, the longer the experiment, the lower the upper confidence limit for extrapolation. This tends to increase the safe level and reward good experimentation.<sup>271</sup> However, because of technical

<sup>268</sup>*Supra* note 208 and accompanying text; *Improved Mantel-Bryan Procedure*, *supra* note 265.

<sup>269</sup>*Supra* note 180 and accompanying text.

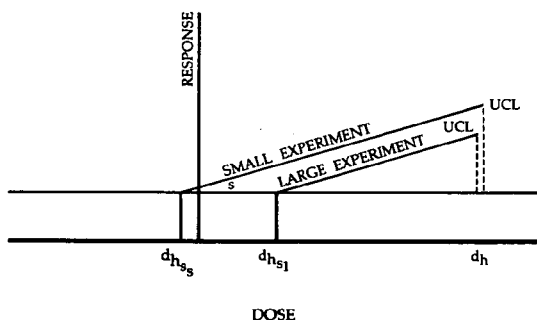
<sup>270</sup>*Supra* note 192 and accompanying text (Dose-Response Curve). The Mantel-Bryan Model uses a Probit Model which allows for a linear rather than sigmoidal curve. *Infra* note 271.

<sup>271</sup>Figure 3.



The UCL is the upper confidence limit which is set at 99%, i.e. 99% of all observed tumors fall below that dose limit. "S" is the maximally permissible risk, i.e.  $10^{-6}$ , and  $d_s$  is the dose corresponding to that risk. At  $d_s$  there is a  $10^{-6}$  probability of carcinogenesis.

Schneiderman and Mantel, *The Delaney Clause and a Scheme for Rewarding Good Experimentation*, 2 PREVENTIVE MEDICINE 165 (1973). The larger the experiment the lower the UCL, thus the higher the safe dose. Figure 4.



$d_h$  — higher dose;  $d_{hs}$  — higher safe doses

problems with the method (e.g., it tends to over-estimate risk in low dose ranges), Mantel-Bryan use is declining.<sup>272</sup> Mechanistic non-threshold models are more scientifically plausible and have undergone refinements, which make them the models of choice.<sup>273</sup> This is because models which incorporate the same diverse biological mechanisms as the cancer process are inherently more accurate.<sup>274</sup> Regardless of what model is chosen, the VSD is multiplied by a safety factor in order to set a safe level.<sup>275</sup>

Quantitative risk assessment, which utilizes chemical data, animal experiments and epidemiologic studies to predict risk of cancer via mathematical modeling, is based on the sound scientific rationale that all chemicals have the potential to induce cancer, and that for most carcinogens there is probably a level which presents a *de minimis* risk.<sup>276</sup> At this time no one model is favored or in different instances workable over another, but by careful analysis of the data, accurate assessments may be made. Whether a full merger with the safety clause is in order is questionable, but there is little sense in making trivial distinctions as to source (*i.e.* food additive versus unavoidable added constituent) when public health is involved. For example, after having explored the cancer processes, a person may determine that exposure to a low level of saccharin may be insignificant in terms of cancer risk compared to exposure to a slightly higher level of aflatoxins. Granted, control of natural constituents, pesticide residues and the like are easier to control than food additives, but this is a problem of risk management not risk assessment.<sup>277</sup> As technology increases and as procedures become more ad-

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<sup>272</sup>Crump, *Theoretical Problems in the Modified Mantel-Bryan Procedure*, 33 *BIOMETRICS* 752 (1977) (model tends to be too conservative); Salsburg, *Open Query: Theoretical Problems in the Modified Mantel-Bryan Procedure*, 33 *BIOMETRICS* 419 (1977).

<sup>273</sup>Mechanistic models include the One-hit, Multistage and Multi-hit models: These models assume that once a single cell has been altered, tumor induction occurs. The most frequently employed model of this category is the Armitage-Doll Model, which takes into account the multi-stage mechanism of carcinogenesis. This too is a conservative model (similar to the Mantel-Bryan procedure) with respect to dose setting. See *Principles*, *supra* note 5, at 10,438.

<sup>274</sup>*Id.*

<sup>275</sup>This procedure insures that the risk of cancer is minimal, the result of these calculations being the Acceptable Daily Intake (ADI). This safety factor is designed to account for differences in interspecies extrapolation and variations in human dietary patterns. *Infra* note 282 (Problems with extrapolation). These safety factors have been used for sometime in predicting no observable effect levels (NOEL). See CASARETT & DOULL, *supra* note 5, at 26 (general discussion of ADI factors and NOEL).

<sup>276</sup>The author realizes that this risk assessment approach will not be applicable in all circumstances, *i.e.* where the additive or regulated substance is potent and of little societal value. *Supra* note 232 and accompanying text. *Supra* note 218 and text accompanying text (potent versus weak carcinogens).

<sup>277</sup>See *Criteria for Chemical Carcinogenicity*, *supra* note 235, at 687 n. 15. (Distinguishes risk as-

vanced<sup>278</sup> their cost will become negligible as compared to the animal studies that are now required.<sup>279</sup> Also, as the data in a library of chemicals expands, the amount of testing required should decrease. Chemical, hence toxicological analogy may supplant some of the more basic studies. After confirmatory studies, the agent may then be regulated based on studies focusing on a specific organ system or biological factor. While quantitative risk assessment is a far superior method to the current Delaney Clause, in technology and concept, some regulatory and social difficulties can be foreseen and deserve consideration.

One such problem concerns "cancer fear." A change in FDA policy without sufficient education/information dissemination to the public could trigger general insecurity. An uninformed citizen could misinterpret the situation as government irresponsibility.<sup>280</sup> These fears may be allayed by simple comparisons of other risks taken in society.<sup>281</sup> Adequate assurances that risk assessments will be conducted appropriately is also beneficial. A fine line must be drawn, however, to ensure that those informed are not lulled into thinking that all cancer risk has dissipated rather than that it is being dealt with responsibly.

A second problem involves extrapolation and concerns both technical and social issues. Ever since toxicity and carcinogenicity testing began, the public has doubted the applicability and accuracy of animal data extrapola-

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ssessment from risk management):

[R]isk management, by definition, begins after risk assessment has determined that a risk to a human population exists. Whereas "assessment" deals with biological significance, "management" deals with the possible alternative regulatory actions. Included in risk management may be evaluations of costs, feasibilities, risk-benefit ratios, availability of replacement substances or processes, and the level of risk that is acceptable to the society in question. Management of risks is a political, social, and economic issue. Scientists acting as scientists have a role in this phase, but it is limited to ensuring that the biological meaning of the risk is understood throughout the process.)

<sup>278</sup>Currently there are computer programs which will aid in the assessment process, hence facilitating calculation and comparison of data. Crump, *On Improved Procedure for Low-Dose Carcinogenic Risk Assessment from Animal Data*, 5 J. ENV. PATHOLOGY AND TOXICOLOGY 675 (1982) (setting water quality criteria using Global 82 computer program).

<sup>279</sup>Animal study costs vary but one commentator places the price approximately at \$75,000 in 1975 for the testing of one chemical for carcinogenesis with one animal species. Note, *Implementing the Anti Cancer Clauses of the Food, Drug and Cosmetic Act*, 44 U. CHI. L. REV. 817, 829 n. 62 (1977).

<sup>280</sup>*Supra* note 231. *e.g.*, "here is the FDA saying in one day all carcinogens are banned because they are inherently unsafe, and the next day allowing them to be added to our food." People also do not want to be that one in a millionth person to get cancer.

<sup>281</sup>*See* CASARETT & DOULL, *supra* note 5, at 713 (*e.g.* risk of being struck by lightning =  $10^{-6}$ , killed in auto accident =  $8 \times 10^{-3}$  (1/8,000), etc. - using 1976 statistics).

ted to man.<sup>282</sup> Because quantitative risk assessment involves two extrapolations, interspecies as well as intraspecies, it may arouse even more skepticism.<sup>283</sup> The use of animal models in predicting human risk has been unduly criticized; in scientific reality there is often little difference systematically between the species.<sup>284</sup> The basic biologic processes are the same, with usually only subtle physiological, anatomical and biochemical differences. Routes of exposure, biodistribution, and mechanism of action (tissue function) differ only slightly from species to species.<sup>285</sup> Metabolism and pharmacokinetics are often different, but much has been learned as to interspecies variability.<sup>286</sup> While some concern is warranted, once these variables have been determined and accounted for, accurate risk assessment is possible. Current research focuses upon interspecies conversion factors for physiologic and biochemical processes and developing dose equivalencies and evaluating the extent to which predictions based on these conversions agree with observed data.<sup>287</sup>

A third concern that must be considered is "risk additivity."<sup>288</sup> Current risk assessment models are based on a certainty of cancer using one compound. A problem arises when more than one compound is present. Summary review of this problem would lead us to believe that the Delaney Clause in its current form would preclude such a situation.<sup>289</sup> This logic appears faulty when it is realized that all compounds carry with them some carcinogenic risk: even if an agent is not a carcinogen *per se* it may influence

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<sup>282</sup>Rall, *Difficulties in Extrapolating the Results of Toxicity Studies in Laboratory Animals to Man*, 2 ENV. RESEARCH 360 (1969).

<sup>283</sup>*Supra* note 259 and accompanying text. Intraspecies extrapolation has been discussed previously and involves high dose to low dose predictions based on curve-fittings.

<sup>284</sup>See CASARETT & DOULL, *supra* note 5, at 120.

<sup>285</sup>*Id.*

<sup>286</sup>Hogan and Hoel, *Extrapolation to Man*, in: PRINCIPLES AND METHODS OF TOXICOLOGY 711 (1982).

<sup>287</sup>*Id.* See also Gillette, *Application of Pharmacokinetic Principles in the Extrapolation of Animal Data to Humans*, 9 CLINICAL TOXICOLOGY 709 (1976).

Also of current interest is predictions of dose based on body surface area rather than body-weight. See Freireich, Gehan, and Rall, *Quantitative Comparison of Toxicity of Anti-cancer Agents in Mouse, Rat, Dog, Monkey and Man*, 50 CANCER CHEMOTHERAPY REPORTS 219 (1966). (mg/kg versus mg/m<sup>2</sup> body surface extrapolation).

<sup>288</sup>See generally Principles, *supra* note 5, at 10,394 (multiple agent exposure).

<sup>289</sup>Theoretically Delaney bans all carcinogens, with certain exceptions, in food. It is these exceptions however, which may cause a problem. Some of those not regulated may create more of a cancer risk than those which are. *Supra* notes 52 and accompanying text (exceptions to Delaney).



the carcinogenic potential of another compound.<sup>290</sup> The problem is complex, especially when the simple adding up of risks most often leads to an inaccurate finding of overall risk. Perhaps the ultimate method of evaluation will hinge upon comparisons of risks and biological activities of the compounds purported to be interacting and adjustments made to the margin of safety used in each. This problem still should not preclude the use of risk assessment as an alternative to the Delaney Clause because it is prevalent in both situations.

As a final consideration it is imperative that pharmacological and pharmacokinetic studies are performed on all compounds, whether under Delaney or otherwise. The administration of compounds in multiples of actual physiological concentration leads to determinations that are inherently incorrect. (e.g. either an under-estimation or over-estimation of risk) If for instance the compound saturates a toxification pathway (*i.e.*, after a certain dose the increase in incidence of tumors over controls levels off) it may appear that the compound is non-carcinogenic after this dose.<sup>291</sup> While adequately conducted tests should expose such a situation, its presence in a study may detract from the credibility it deserves. More important is the reverse situation where saturation of a detoxification pathway occurs. Risk will be overestimated because at these high concentrations it will appear that the compound may have a safe (dose-responsive) level.<sup>292</sup> These toxification/detoxification pathways may include metabolic pathways found in the soft tissues, *i.e.*, liver, lung and kidney; and DNA repair.<sup>293</sup>

### Conclusion

The regulation of carcinogenic substances is not a task to be taken lightly. Analysis of pertinent biologic processes reveals that virtually all substances are potential carcinogens. To differentiate hazardous chemicals that pose significant human risk, quantitative risk assessment promises to supplant

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<sup>290</sup>This is probably best illustrated by the finding that ingestion of alcohol increases the carcinogenicity of benzo(A)pyrene in animals (smoking and drinking alcohol risk). CASARETT & DOULL, *supra* note 5, at 116.

<sup>291</sup>The compound's activity would be similar to the maximal response as seen at the top of the dose response curve. *Supra* note 192 (Figure 1).

<sup>292</sup>*Id.* (If analyzed at a lower dose, a dose-response relation as to cancer induction could result).

<sup>293</sup>*Supra* note 200 and accompanying text (metabolism).

the Delaney Clause and provide a more rational basis for regulating carcinogens. The Delaney Clause has generated considerable controversy since the early 1950's. While banning carcinogenic food additives, food colors, and animal drugs the FDA has seldom employed it. When it has, inconsistent and questionable applications have resulted.

At this point in time it must be conceded that the quantitative risk assessment approach is not perfect, but even in current form it surpasses the current FDA cancer policy. This is due to continuous adherence to the biological processes with which cancer is associated, and the appropriate use of scientific judgment.

Perhaps the most pressing problem besides the adoption of the appropriate procedures is uniformity of policy. Review of the overall cancer process reveals that there is no difference between exposures to carcinogens in foods or from the environment.<sup>294</sup> While there is some interaction in the testing of pesticide and animal drug residues between federal agencies,<sup>295</sup> the regulation of carcinogens has evolved differently and varies widely.<sup>296</sup>

Clearly a more uniform approach is required. Adoption by the FDA of quantitative risk assessment procedures would be a step in that direction. Furthermore, international recognition of the FDA's Good Laboratory Practices and Redbook<sup>297</sup> promise that food standards could be of world wide dimension. It can only be from rational and intelligent decision-making, as well as national and international cooperation, that carcinogenic hazards will be reduced.

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<sup>294</sup>*Supra* note 213 (routes of exposure).

<sup>295</sup>21 U.S.C. § 346a (1970) (the U.S.D.A. sets pesticide tolerances for FDA).

<sup>296</sup>There is a tremendous need for uniformity not only between the agencies but within them. The FDA, for example regulates additives, "added" substances and natural constituents by different means. If this risk assessment proposed is employed for toxicity as well as carcinogenicity testing the system would be much more simplified. The interagency uniformity (or lack thereof) is even more profound. See Principles, *supra* note 5, at 10,428-10,432.

<sup>297</sup>See Redbook, *supra* note 181.

