Toxicologically Insignificant

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Full working draft (2026-06-10). The subject is the de minimis idea in toxicology; John P. Frawley is the protagonist, not the topic. Quotes run long and link to the primary files held in this repository; they will be cut at assembly. Second in the series that began with "Of Mice and Men and Round Numbers." Provenance and evidence grading for every claim are in the numbered dossier (`01_MASTER_DOSSIER.md` and its companions).

This essay is about an idea: that below some level of exposure a chemical is beneath notice and need not be tested at all. The idea is old enough to carry a Latin name, *de minimis non curat lex* — the law does not concern itself with trifles. In toxicology it acquired a number, and the number is what we are after, because of the claim packed inside it. The claim is that there is a line under which not knowing is safe.

We think the claim is wrong, and wrong in a particular way: it fails hardest in the cases where a missed hazard cannot be undone. We will make that argument, and we will also follow the strange career of the idea itself — defeated in the one forum equipped to judge it, then carried past that defeat by a trade campaign, an academy, and finally the federal courts, until a version of the number came to sit in the food-safety codes of two continents.

The idea had a man behind it. He did not invent the wish to stop testing cheap chemistry, but he gave the wish a figure and a phrase, and he makes a useful protagonist because his career runs the length of the whole machine: trained in the laboratory that produced the underlying number, employed by a company that wanted relief from it, seated on the panel that blessed his proposal, and called as the witness whose word later won that company a release in court. His name was John P. Frawley.

1. The number

Through the 1950s Frawley worked in the FDA's Division of Pharmacology under Arnold Lehman, the laboratory that built the two-year feeding study and the hundredfold safety margin — the subject of our first essay. He published with O. Garth Fitzhugh and Arthur Nelson, Lehman's own people. By the mid-1960s he was chief toxicologist at Hercules, the chemical company in Wilmington, Delaware, and he had begun saying in plain terms what the factor of one hundred actually was. From his 1965 paper on rosin (`papers/rosin_1965.txt`; scan here):

> "The original basis for this conservativeness is cited as a device to compensate for our lack of precise means of predicting the effect of a compound on the most sensitive human. I like to call it an 'ignorance factor,' but more traditionally it is called a 'margin of safety.' The figure is based on the assumption that man is 10 times as sensitive as the experimental animals and the most sensitive human is 10 times as sensitive as the average. Experience has taught us that this factor is overly conservative."

This is the seed. The hundredfold margin is an admission of ignorance — a stand-in for knowledge no one had. Frawley's contribution was to argue that the stand-in was too large, and then to build a second number on top of the first. Run the hundredfold margin across a large enough collection of chronic studies, he proposed, and every compound comes out safe at one part per million in the diet. Then divide once more: "protect ourselves by another factor of ten and adopt 0.1 parts per million as a level of toxicological insignificance for all materials other than pesticides and heavy metals" (`papers/f1967.txt`). Below that line, no test. For the manufacturer he restated the diet figure as something readable off a specification sheet — a component present at no more than 0.2% by weight of the container — and filed it with the FDA as a proposed amendment.

The first essay was about a round number reached by multiplying ten by ten. This is the third ten, and it does different work. The margin of safety makes one tested chemical safer. The de minimis number does the opposite: it removes the requirement to test at all, for a whole class of compounds at once. It converts an admitted ignorance into a license to remain ignorant.

2. Proving the obvious

The idea did not arrive as a finding. It arrived as a conclusion in search of support. Frawley opened his 1967 address in London by saying so, more frankly than was prudent (scan here):

> "When was the last time you sat down in the solitude of your study and attempted to write out a geometrical proof that the shortest distance between two points is a straight line? Most of us would have a difficult time doing it today because, as you recall, it is not susceptible to proof. It must be accepted. Indeed, some of the most difficult things in life to prove are the obvious ones. A number of months ago, I sat down to try to prove something which was obvious to me — that there are some uses of food-packaging materials which cannot involve any hazard to health of the consumer of food. I had no preconceived idea of the end point I would reach, but it seemed like it would be fun. Sometimes now I wish I had resisted the temptation and invested my time in some other form of recreation."

He did not set out to learn whether the uses were safe. He set out to prove a thing already held, and to fit it with a number afterward. There is a motive behind the conviction, and it is worth being exact about it because it is the engine of the whole proposal. The 1958 Food Additives Amendment had swept Hercules's food-grade rosins into the class of substances that could not be sold without a two-year study. Frawley did the arithmetic in 1965: "Simple arithmetic of a minimum price of $50,000 per compound times 34 told us we faced an expenditure of 1-3/4 million dollars just for animal studies." To the FDA's own conference in 1968 he put the grievance in the first person (`papers/fdclj_1968.txt`; scan here):

> "I realized that I personally had spent over a million dollars of my Corporation's money investigating the safety of food packaging materials, and from society's point of view it was all wasted, because all were proven to be safe. The benefit to the consumer was zero. The loss to society was a million dollars."

Read that sentence closely, because the de minimis idea lives inside it. It treats a clean result as proof that the test was never needed. It can only reach that judgment by assuming the answer in advance — the studies showed no harm, therefore looking for harm was waste. The cost he resented was real; the testing regime did not scale, and the food supply was changing faster than any laboratory could check it. But the conclusion he drew from the cost was that the looking itself had been the mistake.

3. The objection, stated at its birth

The proposal got its hearing in the one place equipped to judge it, and there it was answered. In February 1968 the FDA convened a National Conference on Indirect Food Additives — called, a trade paper reported, in part "to get a public airing of the complaints before there is a Congressional hearing." The agency's chief scientist, W. H. Summerson, head of the Bureau of Science, devoted his paper to Frawley. He granted "a soundness of certain portions of Dr. Frawley's thesis," then took the central device — one number below which nothing is tested — and called it "sheer nonsense." The reason he gave is the core of the case against de minimis, and it has not weakened (`sources/Summerson_FDA-BureauOfScience_paper_NationalConf_Feb1968_excerpt.md`):

> "Unless premarketing clearance is practiced, the only method of detecting harmful effects is retrospective with respect to exposure to the suspected agent. The latent or 'incubation' period from the time a chemical agent is first applied to the human being until the time that cancer occurs is often 10 years or more … after the 10 year period, with changing food habits, additives and packaging, it is well nigh impossible to isolate an additive as the original causative agent of a cancer. Thus, if we are to give the consumer the protection he expects and demands, we must require premarket testing."

The argument is simple and it is fatal to the idea in its strong form. A threshold of insignificance is set from what is known at the time it is set. The harms that matter most — a cancer that takes a decade to appear, in a population eating a food supply that has changed in the meantime — are exactly the harms that cannot be read off the data in hand. Summerson then named the move underneath the proposal, the substitution of an absence of evidence for evidence of absence:

> "even today we have offered to us a statement to the effect that the proponent feels no food additive clearance is necessary because he has no knowledge of any bad effects from his product."

No knowledge of harm is not knowledge of no harm. That is the whole objection, and the de minimis idea has never answered it. What it did instead was go around it.

4. Around the objection

The idea did not win on the merits in that room; it was carried past the room. In the same paper Frawley reported that "twenty-four other toxicologists from universities and industries have supported this proposal in writing to the FDA," and presented this as spontaneous professional agreement. The industry's own files, recovered decades later, show it as the visible part of an organized effort (`08_VINYL_CHLORIDE_CAMPAIGN.md`). The Manufacturing Chemists Association endorsed the amendment on 3 November 1967, claiming 185 companies and more than ninety percent of U.S. basic chemical capacity; the Society of the Plastics Industry followed three days later. The drafting was run by the packaging-law firm Keller and Heckman, and the plastics committee carrying the proposal was chaired by a Hercules executive, Robert M. Miller. The endorsements were not only evidence of agreement. Frawley's counsel deployed them as a legal argument that the agency had nothing left to decide: the support, he told the conference, "confirms that these uses are generally recognized as safe or 'gras' and that no action on the part of the FDA is necessary."

Then the idea acquired the cover of the Academy. Within a year the National Academy of Sciences took it up and printed Frawley's phrase on the title page. Its Food Protection Committee published *Guidelines for Estimating Toxicologically Insignificant Levels of Chemicals in Food* in 1969 (`papers/nas1969.txt`; scan here). It built on the first essay's number — "the safe level is frequently expressed as 1/100 of the experimentally determined 'no-adverse-effect level'" — and then fixed the line below which a chemical need not be studied at Frawley's 0.1 part per million. The rationale was his:

> "The principle of toxicological insignificance is a valid concept for separating potential health hazards from predictably safe applications. Guidelines on toxicological insignificance are needed to eliminate wasteful diversion of

> scientific resources in university, industry, and government laboratories."

The report cited his 1967 paper, and the drafting task force named in the preface — Smyth as chair, with Coon, Hall, Oser, Schramm, Zapp — included J. P. Frawley. The detail that matters for the idea, rather than the man, is the route: a proposal the FDA's chief scientist had called nonsense became a National Academy recommendation within twelve months, while the objection that had defeated it went unanswered. The proponents held the committee seats.

5. The foundation

An idea that exempts chemicals from testing is only as good as the evidence that it is safe to do so, and here the foundation deserves a look, because the man advancing the idea was also a supplier of its data. Frawley's 1967 appendix rested in part on unpublished work from Hercules, his employer, and from Industrial Bio-Test Laboratories, the contract house Hercules used — whose president, Joseph Calandra, was Frawley's repeated co-author across the decade. IBT is not a neutral citation. When the EPA finished auditing its pesticide files in 1983 it found, of "801 studies on 140 pesticides" in the reviewed categories, that "594 (74%) have been found invalid" — animals recorded as examined after death, results adjusted or invented (`papers/ibt_review_1983_ocr.txt`). It was the largest data-fraud scandal in the history of product-safety testing.

Fairness requires the correction that the easy version of this gets wrong, and the correction is in `09_IBT_FRAWLEY_OVERLAP.md`. The de minimis dataset was not, in the main, built on the fraudulent studies. Only four of the roughly 220 compounds in the appendix cite IBT, and all four are color additives outside the pesticide audit; the pesticides Frawley listed he cited to Lehman's FDA compilations, which predate IBT's pesticide work and in several cases trace to studies Frawley himself ran at the FDA. The point against de minimis here is not that its arithmetic was forged. It is structural: a deregulatory proposal that would relieve a company of testing costs was advanced by that company's toxicologist, on a base that drew partly on that company's own unpublished data and on a contract laboratory later convicted of inventing results. The idea was never examined at arm's length from the interest it served.

6. Where the idea breaks

Time was the test the idea could not pass, and it failed in the place its own logic was weakest. Frawley had divided his world into the dangerous — pesticides and heavy metals, carved out by name — and everything else, the packaging chemistry he was defending. The highest no-effect value in his 1967 appendix belonged to that second class: a vinyl chloride–vinyl acetate copolymer, listed safe at 120,000 parts per million. Vinyl chloride monomer, the reactive species that copolymer sheds, is now an IARC Group 1 human carcinogen, the cause of a rare liver cancer in the men who polymerized it; within six years of his talk the workplace limit fell from 500 parts per million to one. The one compound in his

"all other" group that he himself flagged — "the only compound," he wrote, "which was toxic below 100 ppm" — was acrylamide; he listed it safe at 40 and moved on. Acrylamide is now IARC Group 2A, genotoxic through its metabolite, and forms in cooked food. The full table is in `09_IBT_FRAWLEY_OVERLAP.md`.

Cyclamate closes a longer loop and shows the idea failing in slow motion. As a young FDA man in 1951 Frawley co-authored the study that judged "saccharin and sodium cyclohexyl sulfamate had only slight effects at a dosage level of 5 percent" (scan here). Sodium cyclohexyl sulfamate is cyclamate. He carried it into his 1967 list as safe. In October 1969, twenty months after the FDA conference, the agency pulled cyclamate from American food over bladder tumors in rats.

These are not only cases of a number set too low. Under the strongest of them is a flaw in the unit itself. For a genotoxic carcinogen — vinyl chloride, acrylamide — the working assumption today is that no dose does nothing; the modeled risk runs down to a single molecule. The no-effect level, the quantity Frawley's entire table was built from, is not a property these chemicals possess. The de minimis idea depends on there being a threshold below which exposure is meaningless. For the very class of hazard that Summerson warned about — the slow, irreversible carcinogen — that threshold does not exist, and so the idea is not merely too generous there. It is a category error. We should not overstate it: several of the lost colorants were delisted as unsafe rather than classified as carcinogens, and cyclamate's mechanism is still argued. The clean cases are vinyl chloride and acrylamide, and they are enough, because they are precisely the cases the threshold was supposed to cover and the cases in which being wrong is permanent.

7. The idea defends itself

When the IBT fraud forced a reform — the FDA's Good Laboratory Practice rules, the record-keeping standards meant to make an invented study harder to file — the response from the idea's camp was not to concede that trust had been misplaced. It was to attack the reform. Frawley's 1981 article for the new journal *Regulatory Toxicology and Pharmacology* is the clearest statement of the posture (`papers/f1981.txt`; scan here):

> "For the regulatory agency, GLPs merely refer to proof that there was no cheating in the experiment … Only a few years ago, we were willing to take this for granted. We had mutual trust in each other, scientist to scientist … It is a sad commentary that the signatures and reputations of all of us in this room are not sufficient in the judgment of the regulatory agencies to validate a study. A reputation, built on a career of integrity, is worth nothing today. Peer review has been replaced by peer intimidation."

The rules he objected to existed because a laboratory tied to him had been caught fabricating data. The same article argued against "zero risk" and "the Delaney philosophy" and for a tolerable, calculable threshold of harm — the de

minimis idea in its mature form. Its defense, when the evidence base under it collapsed, was to insist that the toxicologist's word should still be enough. That is the same substitution Summerson had named in 1968: take the absence of a finding for proof of safety, and take the offer of it for clearance.

8. It became law

The idea failed at the FDA and won everywhere else, and the legal route is the part most often left out of the story. The full reconstruction is in `10_DE_MINIMIS_LEGAL_LINEAGE.md`.

Inside the agency the proposal died. The FDA's own Dr. Ramsey drafted a version — an exemption for substances migrating below fifty parts per billion — and in June 1971 the agency set it aside, judging that the statute did not let it exempt a chemical that met the literal terms of the "food additive" definition. The authority it believed it lacked was then supplied by a court. In *Monsanto Co. v. Kennedy*, 613 F.2d 947 (D.C. Cir. 1979), a case about acrylonitrile migrating from a plastic beverage bottle, the D.C. Circuit ruled (`sources/Monsanto-v-Kennedy_613F2d947_DCCir-1979_opinion_CourtListener.txt`):

> "There is latitude inherent in the statutory scheme to avoid literal application of the statutory definition of 'food additive' in those de minimis situations that, in the informed judgment of the Commissioner, clearly present no public health or safety concerns. Thus, the Commissioner may determine based on the evidence before him that the level of migration into food of a particular chemical is so negligible as to present no public health or safety concerns …"

Co-petitioner beside Monsanto was the Society of the Plastics Industry — the same trade group that had carried Frawley's proposal to the FDA eleven years earlier. The doctrine the industry could not win from the agency it won from the bench.

The courts also marked the doctrine's limit, and the limit is the most revealing thing about it, because it is an admission that the idea fails where Summerson said it would. Twice — over carcinogenic dyes in 1987, over carcinogenic pesticides in 1992 — the courts refused to read a trivial-risk exception into the Delaney Clause, the 1958 bar on any food additive shown to cause cancer. In *Public Citizen v. Young*, 831 F.2d 1108 (D.C. Cir. 1987), the FDA had cleared two dyes whose lifetime cancer risk it estimated at "one in 19 billion" and "one in nine million." The court struck the clearances down (`sources/PublicCitizen-v-Young_831F2d1108_DCCir-1987_opinion_law.resource.org.html`):

> "Here, we cannot find that exemption of exceedingly small (but measurable) risks tends to implement the legislative design of the color additive Delaney Clause. The language itself is rigid … We conclude, with some reluctance, that the Clause lacks such an exception."

Les v. Reilly, 968 F.2d 985 (9th Cir. 1992), held the same for pesticide residues. So the law itself draws the line exactly where the idea breaks: de minimis is allowed for everything except the carcinogens. But notice the catch in how the exception is written. When the FDA finally codified the threshold in 1995 — the Threshold of Regulation rule, which exempts a food-contact substance whose use stays "at or below 0.5 parts per billion" — it conditioned the exemption on the substance "not having been shown to be" a carcinogen (`sources/FDA_Threshold-of-Regulation_60FR36582_1995.txt`). The word doing the work is *shown*. The whole purpose of the threshold is to skip the testing that would show it. A carve-out for known carcinogens, attached to a rule designed to let chemicals through untested, protects against the hazards already found and leaves the unfound ones exactly where they were. This is Summerson's objection, now built into the regulation that overrode him.

The rule rests its authority on *Monsanto* and states the principle in a footnote in Latin — *de minimis non curat lex* — the same tag Frawley used to the FDA in 1968. It credits the FDA scientist who revived the idea in 1987, Alan Rulis, who had given Frawley his due in a single line: the pattern was "actually not new at all, having been observed and duly noted by Frawley in 1967, using a different data base" (`sources/Rulis_1987_DeMinimis-Threshold-of-Regulation_textViaJina.txt`). The rule does not name Frawley. The number then traveled on — into a European database of several hundred chemicals and into the Threshold of Toxicological Concern that the food-safety systems of two continents now use. How a no-effect level hardened into a no-test threshold for whole classes of chemistry is a longer story, and a later one. What the FDA's chief scientist called sheer nonsense in 1968 is now routine.

9. The two registers

There is one more document, and it indicts the de minimis posture as a posture. The same actors who told the public that the chemistry of commerce was beneath notice did not, among themselves, believe that knowledge was beside the point. They believed exactly the opposite, and acted on it.

On 19 March 1965 V. K. Rowe of Dow Chemical wrote to a short list of manufacturers — Monsanto, Hooker, Diamond Alkali, and Hercules's Frawley — to convene a meeting about "highly toxic impurities" in 2,4,5-trichlorophenol, the building block of the herbicide 2,4,5-T (Poison Papers, Bates B 1575; `sources/PoisonPapers_B1575_Rowe-to-Frawley_1965-03-19.txt`). The impurities were dioxins. Four months later Frawley wrote up a telephone call on a memo he marked Confidential; it survives because an Agent Orange brief reproduced it (`toxicdocs/3unclear__xxxx__na__Dioxin__jyBDvYGzG58gkKk3VmDbjxLK5.txt`):

> "Mr. Farnham was convinced that no one else in the industry had done anything to remove the contaminant from their 2,4,5-T. Mr. Farnham further stated that Dow was extremely frightened that this situation might explode. Mr. Frawley quotes Mr. Farnham as stating that Dow [was] 'aware that their competitors are marketing 2,4,5-T which contains alarming amounts of

> acnegen and that if the government learns of this the whole industry will suffer. They are particularly fearful of a congressional investigation and excessive restrictive legislation on the manufacture of pesticides which might result.'"

The public file is written in the vocabulary of trifles and insignificance. The private file is written in the vocabulary of a fire alarm. The two concern different chemistries — packaging resin and herbicide — and the qualifier in Frawley's favor is real and has to be given full weight: Hercules's own 2,4,5-T sat at the clean end of the industry, and the court that later reviewed the record found no measurable dioxin in it but for a single 1966 trace. In the memo he is recording the industry's fear, not confessing his company's guilt. That is what makes it a clean specimen of the two registers the de minimis posture requires. In public, the claim that exposure below a line is meaningless; in private, an industry that understood precisely how much a hidden hazard could cost, and how badly it did not want the government to look.

The registers met in court. When the Agent Orange cases reached summary judgment in 1983, it was Frawley's sworn testimony that Hercules's product was at the clean end which won the company its release on the government-contractor defense (*In re "Agent Orange,"* 565 F. Supp. 1263; `sources/565_F.Supp.1263_AgentOrange_1983_opinion.txt`). Chief Judge Weinstein withdrew that ruling before it became final, and the case settled in 1984. The record does not show that Frawley lied. It shows the same instrument used twice: the cleanest available reading of the facts, offered first to argue that chemicals were beneath the law's notice and then to argue that a company was beyond a lawsuit's reach.

Coda

The case for the de minimis idea was never empty. The testing requirement did not scale; the food supply was changing faster than anyone could check it; for many ordinary compounds the hundredfold margin really was conservative, and a rule that let trivial migrants through without a two-year study saved real money and real animals to no obvious cost. We do not think the people who built it were villains, and the man at the center of this one held the view in good faith for twenty-five years. The reckoning is with the idea, not with him.

And the idea is a license not to know. It takes a number set from present knowledge and treats it as a boundary on future harm. It works for the hazards that announce themselves quickly and fails for the ones that arrive slowly and cannot be reversed, which are the hazards that most need a rule. Its central unit, the no-effect level, does not exist for the genotoxic carcinogen; for that class the threshold measures something the chemical does not have. The law that adopted it conceded as much, carving out the known carcinogens — and then conditioned the exemption on a showing that the threshold itself is designed to avoid making.

The two threads run as they did in the first essay. The science kept getting less ignorant. It learned that vinyl chloride causes a cancer no two-year study at a "safe" dose would catch, the latency Summerson described in 1968 and was

talked past. It learned that the no-effect level is not the right quantity for a genotoxic carcinogen. It learned, in the IBT scandal, what the era's data was worth. The regulation did not keep pace. The doctrine called sheer nonsense was beaten at the FDA, granted by the courts, written into the federal code, and exported to Europe, and several of the chemicals it was built to excuse were banned along the way while the framework that excused them was not.

The first essay could close in its subjects' own words, because the men who set the factor of one hundred turned on their own number late in life — "we maybe got the figure first, then justified it secondly." This one cannot. What the de minimis idea left in its author's own words is not a second thought but a complaint: that he had spent a million dollars proving food packaging safe, and "from society's point of view it was all wasted." The sentence assumes its conclusion and resents the question. Some of the trifles mattered. One was a plastic rated safe at 120,000 parts per million, and the monomer it sheds gives men liver cancer. The law, it turned out, had reason to concern itself with trifles.

Primary files are linked inline and held in `papers/`, `sources/`, and `toxicdocs/`. Evidence grading, alternative readings, and open questions are in `05_OPEN_QUESTIONS.md` and the numbered dossier.