Frequency of Submission of Toxicity Information on Premanufacture Notices

6. Frequency of Submission of Toxicity Information on Premanufacture Notices

The legislative history of the Toxic Substances Control Act (TSCA) emphasizes that Congress was interested in toxic substances being identified before they enter commerce. And, of course, the most direct and immediate way of learning about toxicity is from toxicologic tests.

There are two reasons for toxicologic information appearing in a premanufacture notice (PMN) file; it could have been submitted on the original PMN, or it could have been requested by the Environmental Protection Agency (EPA). There are two avenues for request: a formal 5(e) order under TSCA, or an "informal" request with which the submitter complies.

OTA inspected each PMN for 11 items about toxicity that appear on the European Economic Community (EEC) Minimum Premarketing Data (MPD) set **(46** F.R. 8986) of required premarket testing information. Table 10 lists those items and describes their uses in risk assessment. (One toxicity item listed by EEC, a determination of any lethal effect of the substance on algal growth, was not recorded by OTA). The summary of toxicity concerns addressed in EPA's initial review of PMNs (app. A) lists many of the specific tests scored by OTA. When a test result was not reported, and that test was of importance to EPA's risk assessment, EPA scientists would have had to estimate the chemical's toxic effects based on Structural Activity Relationship (SAR) analysis.

The first three items listed on table **10,** acute toxicity tests, are similar in that they measure the lethality of the substance in laboratory animals; they differ in routes of exposure. Contact irritations and sensitizations, whether of the eye or the skin, are common problems in the workplace and in consumer uses. The two skin tests and one eye test provide estimates of the effects from short-term exposures of those organs. Repeated dose toxicity tests employ repeated doses at a level not known to cause death and measure the effects on organ systems.

Mutagenicity is the capacity to cause changes in the genetic material, DNA. Most tests for mutagenicity are "short-term" or "in vitro tests," which require a few days to a few weeks for execution and measure interactions between the chemical and DNA (11). Table 11 is a description of eight general types of short-term tests useful for measuring mutagenicity or other interactions with DNA.

Table 10.—Items of Toxicity Information That Were Scored on PMNs

Item/Usefulness in determining possible risks of chemicals
Acute oral **toxicity.—Provides information from animal tests about possible lethal or other serious effects from short-term ingestion.**
Acute dermal toxicity. **—Provides information from animal tests about possible lethal or other serious effects from short-term exposures on the skin.**
Acute inhalation **toxicity.— Provides information from animal tests about possible lethal or other serious effects of short-term inhalation.**
Skin **irritation-Provides information from animal tests about possible irritation resulting from contact with the skin.**
Skin **sensitization.—Provides information from animal tests about possible changes in the skin resulting in increased sensitivity to other substances.**
Eye irritation. **—Provides information from animal tests about possible adverse effects from the substance reaching the eye.**
Repeated dose **toxicity.—Provides information from animal tests about effects of repeated exposures on major organ systems.**
Mutagenicity.– **Provides information from tests on microorganisms, animals, or cells from various organisms about the possible mutagenicity of the chemical.**
Fish toxicity.—Provides information about possible adverse effects on fish.
Daphnia toxicity.— **Provides information about possible adverse effects on invertebrates.**
Biological accumulation/degradation. **—Provides information about the tendency of the chemical to be accumulated or to be degraded in biological systems.**
Miscellaneous.—Some PMNs included additional information from other toxicity tests and other sources.

SOURCE: In part from Mazza (1982); OTA (1981); Office of Technology Assessment.

Table 11.—Eight General Classes of Short-Term Tests That Measure Mutagenicity or Other interactions With DNA

1. Mutagenesis in bacteria and bacterial viruses.
2. Mutagenesis in yeast.
3. Mutagenesis in cultured (laboratory-grown) mammalian cells.
4. Mutagenesis affecting mouse hair color.
5. Mutagenesis in fruit fries *(Drosophila* melanogaster).
6. Effects on chromosomal mechanics in intact mammals and in mammalian cells in culture.
7. Disruption of DNA synthesis and DNA repair mechanisms in bacteria and other organisms.
8. in vitro transformation of cultured cells.

SOURCE: Off Ice of Technology Assessment (1981).

TSCA focused attention on three kinds of toxicities-carcinogenicity (the capacity to cause cancer), mutagenicity, and teratogenicity (the capacity to cause birth defects). Such "chronic toxic effects" can result from low dose exposures. Mutagenicity (certainly), carcinogenicity (generally), and teratogenicity (perhaps) result from interactions between environmental agents and DNA. Of the toxicity tests listed in table 10, only mutagenicity tests measure interactions with DNA and bear directly on questions of chronic toxic effects. Other tests for chronic toxic effects, involving large numbers of experimental animals, long periods of time, and high costs (9) are considered too expensive for new chemicals.

Fish and daphnia toxicity tests provide information about "ecotoxicity." They are especially useful in making projections about the effect of the chemical on aquatic organisms.

Biological accumulation and degradation tests provide important information about the persistence of the chemical in organisms and biological methods for degradation. The value of these tests is greatest for substances to be discharged into water, and industry reviewers of the first draft of this report pointed out that such tests are not necessary on substances that will not reach a water source. OTA did not collect information about whether or not it was planned to discharge chemicals described on PMNs into water, and so cannot comment on the appropriateness of ecotoxicity data submission.

HOW MANY TOXICOLOGIC DATA WERE SUBMITTED ON PMNs?

The number of PMNs containing toxicity information is shown on table 12. Overall, 53 percent of all PMNs inspected had some information about toxicity. PMNs that described manufactured chemicals had such information somewhat more frequently; 59 percent reported some toxicologic information. As a group, the June 1982 PMNs reported toxicity data less frequently than

Table 12.-Number of Toxicologic items Submitted on PMNs

	Manufactured		Non-manufactured		June 1982		Regulated	Total	
	No.	Percent	No.	Percent	No,	Percent	No.	No.	Percent
PMNs	331	100	330	100	70	100	9	740	100
Acute oral toxicity	165	50	126	38	25	36	1	317	43
Acute dermal toxicity	132	40	75	23	13	19	0	220	30
Acute inhalation toxicity	33	10	28	8	4	6	0	65	9
Skin irritation	124	37	101	31	21	30	1	247	33
Skin sensitization	40	12	23	7	3	4	0	66	9
Eye irritation	137	41	115	35	20	29	1	273	37
Repeated dose toxicity	56	17	28	8	0	—	1	85	11
Mutagenicity	58	18	55	17	11	16	2	126	17
Fish toxicity	35	11	26	8	1	1	2	64	9
Daphnia toxicity	16	5	12	4	1	1	0	29	4
Biological accumulation or biological degradation	20	6	12	4	4	6	0	36	5
No toxicity information	137	41	167	50	37	53	6	347	47

SOURCE: Office of Technology Assessment.

did the manufactured or nonmanufactured PMNs.

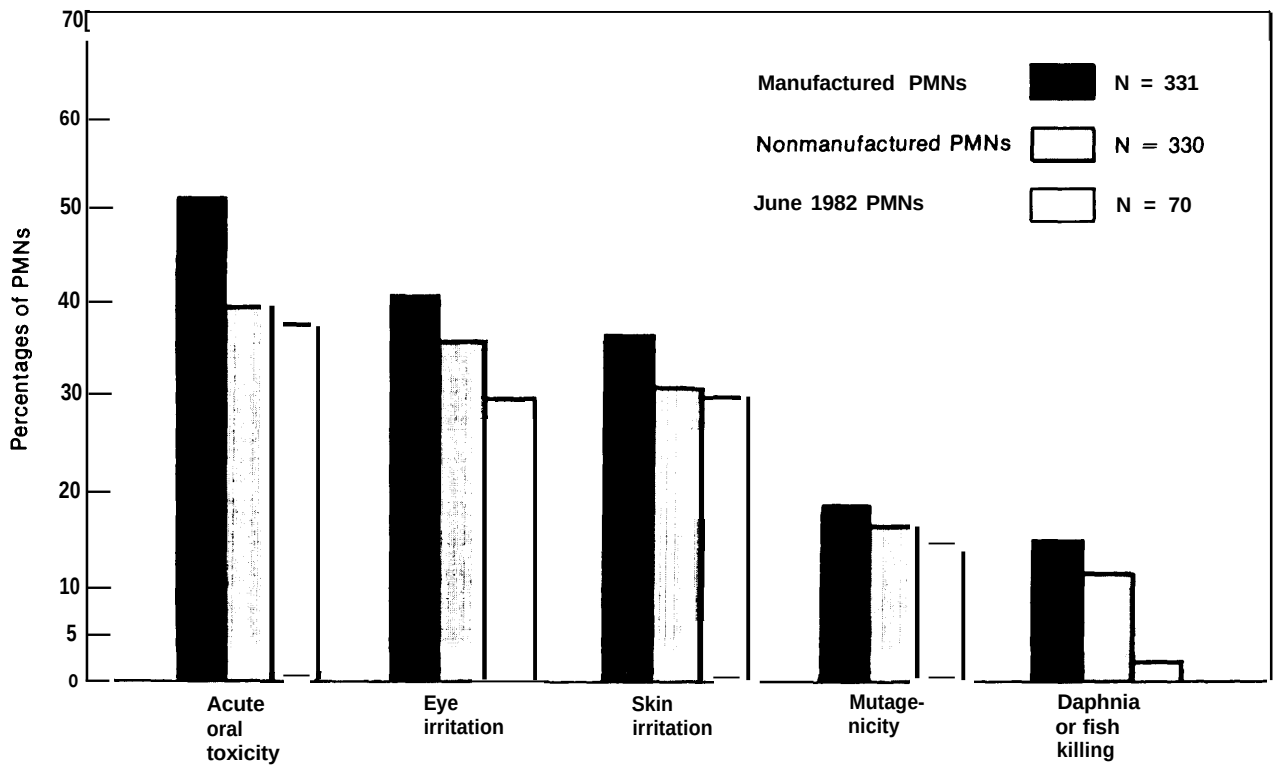
The most frequently reported toxicity tests were acute oral toxicity tests that establish the lethality of the chemical when ingested by test animals. Fifty percent of the manufactured PMN chemicals and **43** percent of all PMNs contained that kind of information. The second most frequently reported test was for eye irritation, followed closely by tests for acute dermal toxicity and skin irritations.

Mutagenicity tests, the only tests that bear on chronic toxicity, were reported on less than one-fifth (17 percent) of all PMNs. Data about ecotoxicity were reported even less frequently: fish toxicity on 9 percent of PMNs; daphnia toxicity on 4 percent; biological accumulation or degradation on 5 percent. Figure 5 is a comparison of the frequency of submission of the three most commonly reported toxicity tests and mutagenicity tests on manufactured, nonmanufactured, and June 1982 PMNs.

TSCA is written to protect against unreasonable risks to human health or the environment, and PMNs contain limited data for EPA to consider in making decisions about potential chronic toxicities or ecological toxicity. Several reviewers of the first draft of this background paper pointed to the absence of such data as a major concern. EPA can use SAR analysis to make estimates of toxicity when data are not available, but whether EPA appropriately decides that SAR analysis is sufficient can be questioned. At a more fundamental level, given the limited experience with SAR, the appropriateness of the technique can also be questioned. Unquestionably, however, it is employed.

The reduced toxicity submissions in June **1982** may be only a "blip," an abnormally low month, or it may reflect a downward trend over the peri-

Figure 5.—Percentage of PMNs Containing the Three Most Commonly Reported Toxicity Tests and the Two Tests Related to Chronic Toxicity and Ecotoxicity



SOURCE: Office of Technology Assessment.

od June 1981 to June 1982. The observed drop in reporting of all toxicity information items was not paralleled by a drop in physical-chemical data reporting. June 1982 PMNs were highest in the frequency with which 4 of the 11 physical-chemical items were reported (see table 7).

A number of reviewers objected to drawing even a tentative conclusion from comparing the June **1982** data to earlier data. One group of industry reviewers inspected the publicly available records for the June **1982** PMNs and provided its appraisal of those for which no toxicity information was reported. According to the opinions of those industry reviewers, the June **1982** PMNs that contained no toxicity data described chemicals that were not hazardous.

Another reviewer (not from an environmental group), drew a very different conclusion from the comparison of June **1982** data to earlier data. In his opinion, if the decrease in toxicity data reporting is general and not confined to the single month of June 1982, it reflects an industry perception that EPA is no longer so serious about PMN reporting. In turn, that perception of decreased EPA concern about new chemicals is being translated into reduced industry attention being paid to learning about potential toxicity.

TOXICITY DATA WERE MORE FREQUENTLY REPORTED ON MANUFACTURED PMNs

Just as was found for physical-chemical data, PMNs describing now-manufactured chemicals contain more toxicity information than PMNs for substances not yet manufactured. The same sort of analysis described in table 8 was applied to toxicity data. As is shown on table 13, there is no consistent relationship between time required for commencement of manufacture and amount of submitted toxicity information. Therefore, although more toxicity and physical chemical data are reported for manufactured PMNs, the completeness of reporting does not appear to be a function of how close to manufacture the substance was when the PMN was submitted. Instead, these observations may suggest that submitters' analyses permit them to judge accurately which substances are more likely to be manufactured and to produce more information about them.

Table 13.—Completeness of PMNs for Toxicity Information as a Function of the Time Between End of the Review Period and the Commencement of Manufacture

	Time to notice of commencement													
	<1 day	1-9 days		10-29 days		30-89 days		90-119 days		120-179 days		160-365 days		>365 days	
	No.	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent
PMNs	10	45	100	41	100	87	100	23	100	41	100	58	100	25	100
Acute oral toxicity	3	29	44	17	41	50	57	10	43	20	99	26	45	19	76
Acute dermal toxicity	3	19	42	12	29	38	44	10	43	13	30	24	41	13	42
Acute inhalation toxicity	0	5	11	7	17	10	11	1	4	3	7	4	7	3	12
Skin irritation	3	14	31	13	32	36	41	9	39	13	30	23	40	13	42
Skin sensitization	0	4	8	7	17	7	8	6	26	4	10	8	14	4	12
Eye irritation	2	18	40	14	34	42	48	8	35	14	34	23	40	16	48
Repeated dose toxicity	0	3	6	5	12	12	14	5	22	8	20	12	21	11	44
Mutagenicity	1	3	6	7	17	15	17	5	22	4	10	19	33	4	16
Fish toxicity	1	4	8	3	7	9	10	4	17	3	7	7	12	4	16
Daphnia toxicity	1	0	–	2	5	2	2	3	13	1	2	4	7	3	12
Biological accumulation or biological degradation	0	3	6	1	2	7	8	0	–	4	10	3	5	2	8

SOURCE: Office of Technology Assessment.

SUBMISSION OF TOXICITY DATA ON PMNs DESCRIBING DIFFERENT CLASSES OF CHEMICALS

As a class, polymers are associated with less hazard than some other chemicals, and some substances of this class are being proposed for exemption from PMN review by EPA (see table 2). In many cases, the large size (high-molecular weight) of polymers makes them biologically inactive because they cannot be taken up by most cells. For that reason, EPA considers toxicity information to be of less importance for Class 3 chemicals (polymers) and of more importance for the Class 1 and 2 chemicals.

Table 14 shows the frequency, by class of chemical, with which toxicologic information was submitted on PMNs, and figure **6** shows the frequency of submission of the three most common toxicity items and mutagenicity and ecotoxicity. In keeping with the inherently lower toxicity of polymers, less testing was reported for those substances.

More importantly, perhaps, removing Class 3 chemicals, polymers, from consideration allows computation of the frequency with which toxicity data for Classes 1 and 2 are submitted. Sixty-one percent of nonpolymer PMNs reported acute oral toxicity data, eye irritation was reported on **52** percent, and skin irritation on 49 percent. Mutagenicity data, important to making estimates of chronic toxicity, were submitted on 27 percent of Classes 1 and 2 PMNs and fish toxicity and daphnia toxicity on 13 and 5 percent respectively (table 14).

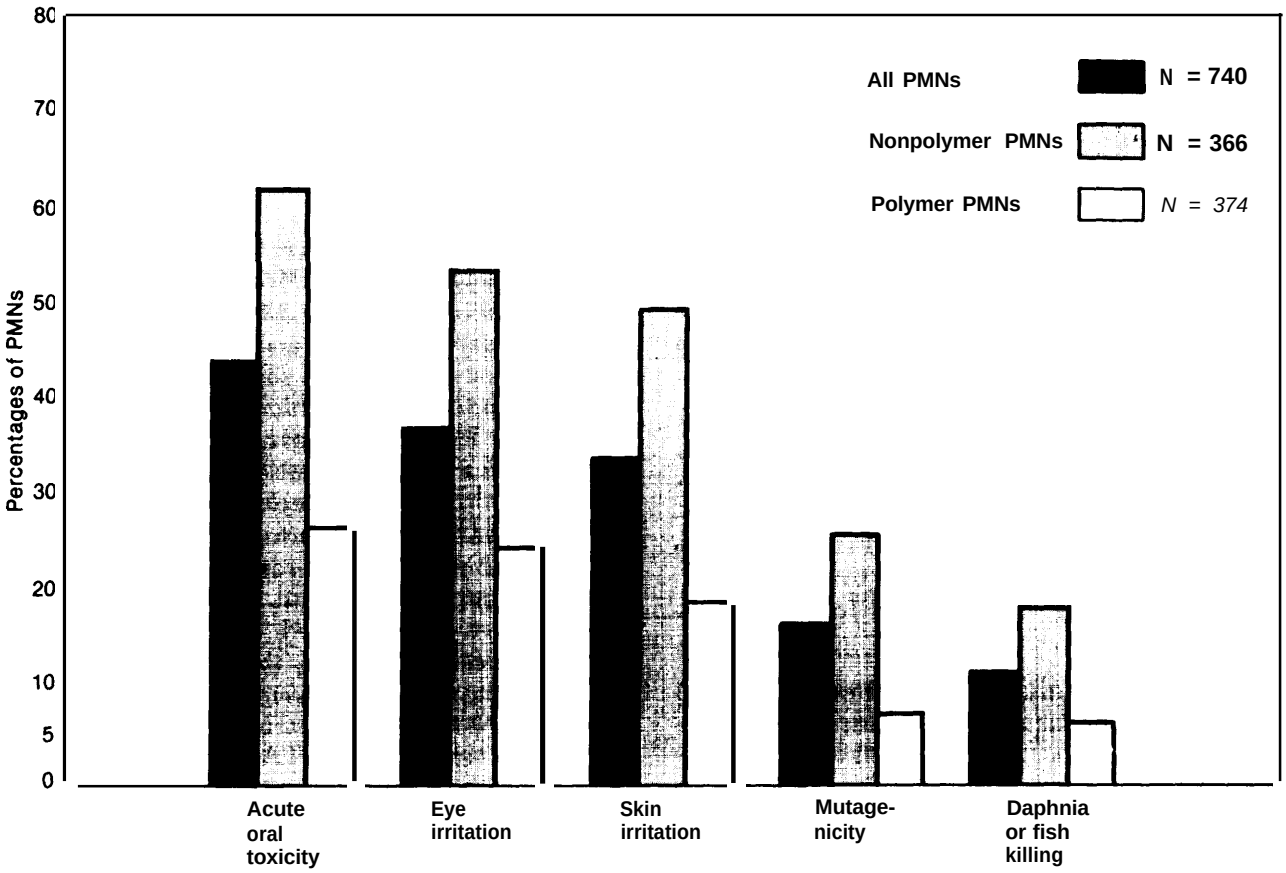
If the proposition is accepted that toxicity data are less likely to be needed for evaluating polymer PMNs, the data in table 14 can be taken, with some caveats, as a more accurate representation of frequency of toxicity submission. However, some monomers from which polymers are made are toxic. If a polymer preparation is contaminated with a significant fraction of free monomers or low-molecular weight polymers, toxicity information would be important. Polymer PMNs sometimes report the percentage of monomers present, but OTA did not attempt to correlate percentages of monomeric and low-molecular weight contamination with submitted toxicity data. By the same token, some of the Class 3 polymers PMNs that submitted toxicity data reported monomer toxicity, but OTA did not record those details. In addition, reviewers of the first draft of this report drew attention to the possible contamination of polymers with catalysts and other chemicals used in their manufacture.

Table 14.—Toxicity Information on PMNs Describing Class 1, Class 2, and Class 3 Chemicals

	Class 1		Class 2		Class 3		Class 1 and Class 2	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent
PMNs	293	100	73	100	374	100	366	100
Acute oral toxicity	178	61	44	60	96	26	222	61
Acute dermal toxicity	120	41	33	45	68	18	153	42
Acute inhalation toxicity	34	12	8	11	24	5	42	11
Skin irritation	147	50	32	44	69	18	179	49
Skin sensitization	42	14	8	11	16	4	5 0	14
Eye irritation	153	52	36	49	85	23	189	52
Repeated dose toxicity	52	18	10	14	24	6	62	17
Mutagenicity	82	28	16	22	28	7	98	27
Fish toxicity	43	15	5	7	16	4	48	13
Daphnia toxicity	20	7	0	–	9	2	20	5
Biological accumulation or biological degradation	25	9	4	5	7	2	29	8

SOURCE: Office of Technology Assessment.

Figure 6.-Percentage of Polymer and Nonpolymer PMNs That Contained the Three Most Commonly Reported-Toxicity-Tests and Tests Related to Chronic Toxicity and Ecotoxicity



SOURCE: Office of Technology Assessment.