A Case Study: Polychlorinated Biphenyls

Edward J. Burger, Jr., M.D., Sc.D.
Office of the President's Science Adviser, Science and Technology Policy Office, Washington, D.C.

ABSTRACT

The Government "decisions" on polychlorinated biphenyls (PCBs) constituted an unusual regulatory exercise compared to much of the experience of the past few years.[1] *PCBs had been developed in the late 1920s to serve in instances where high physical and chemical stability were advantageous. In part, precisely because of these peculiar properties, they became recognized as particular environmental hazards. The processes of analysis and study by the Government for decision were fuller and more deliberate than is often the case. A number of scientific reviews were joined in the process. Benefits as well as hazards were explicitly considered. Regulatory type action was not taken until suitable information was marshalled and recent scientific evidence was given the benefit of interpretation. Finally, the process of deliberation was an unusually open one with the results of analysis fully displayed.*

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[1] In February 1975, the National Academy of Sciences organized a working conference to explore the process of Government decision-making to regulate chemicals in the environment. To assist this conference, a series of case studies of past regulatory decisions was solicited from persons who had reasonably detailed knowledge of them. What follows is the case study of polychlorinated biphenyls as one of the series used in the NAS study. The majority of the Government pronouncements and decisions in this instance derived from a series of studies and analytic exercises convened by the Office of the President's Science Adviser. (This study is also to appear as a part of a book by the author on regulation and human health, to be published by Lexington Books, Inc.)

INTRODUCTION – NATURE OF THE DECISION

The process of Federal Government deliberation and decision on polychlorinated biphenyls (PCBs) was relatively circumscribed and straightforward. The Government actually possessed little in the way of legal, regulatory authority. Hence, the "decisions" leaned heavily on persuasion and on para regulatory moves. Nevertheless, the Government's decisions in this case did lead to the intended and recommended actions (reduction and restriction in certain uses of PCBs) and a tightening of the procedures governing the manufacture, importation and continued use of these chemicals.

Most important, perhaps, was the fact that the decisions and actions assumed by the Government (and by parts of the private sector) were taken deliberately and on the basis of unusually good analysis and information. The PCB decisions, in brief, were unusually well informed decisions when compared to others of this type, and the analyses used to arrive at the decisions were probably fuller and of a higher quality than is the case with most regulatory actions.

The several agencies of the Federal Government concerned with the PCB question contributed to the deliberations and to the analyses. At the same time, an outside group of scientific experts was engaged by the Office of Science and Technology to consider PCBs from a broad perspective as a case study of a hazardous substance existing in the environment in trace quantities. The Government's major deliberative body for its decisions was an interagency, PCB Task Force – run jointly by the OST and the CEQ. The case study of the outside advisers to the OST was timely and useful to the Government's own analyses.

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THE ENVIRONMENT – OFTEN DISTANT FROM APPARENT SOURCES

PCBs were among the materials found, but when analysed they were often confused with other substances. PCBs were first distinguished from the "unknown interfering compounds" found in nature in 1966 by Jensen[2] and the next year by Widmark.[3] On the basis of this latter report, the Food and Drug Administration was moved to develop analytic methods to distinguish between PCBs and chlorinated organic pesticides encountered in monitoring for regulation.

In February 1969, Dr. Robert Risebrough gathered attention by warning, in an article in the *San Francisco Chronicle*, of the dangers of PCBs in the eco-system. Over the next 6–7 months, the FDA increased its surveillance of foodstuffs for evidence of PCB residues. Notable positive findings were in fish. Monitoring of foodstuffs, raw agricultural products, fish, and feeds for PCBs was augmented throughout 1970. PCBs were found in fish and in marine animals in high concentrations close to plants which manufactured the chemical.

ACCIDENTAL SPILLS OR LEAKAGES OF LARGE QUANTITIES OF POLYCHLORINATED BIPHENYLS WITH CONSEQUENT CONTAMINATION OF FOODSTUFFS AND ANIMAL FEEDS.

In 1968, PCBs, used as a heat-exchange fluid in a pasteurizer, leaked into rice oil being manufactured for home cooking use in a plant in Japan. More than 1,000 persons were affected by the contaminated rice oil, many of whom exhibited persistent skin lesions as well as systemic disease (Yusho disease). In July 1971, leakage of heat exchange fluid caused contamination of pasteurized fish meal which was used as a feed ration for chickens and catfish.

In addition to these two major areas of concern, PCBs began to be reported with increasing frequency in poultry and in eggs, and in packaging material for food.

PCBs appeared with increasing frequency in 1970 and 1971 in the professional scientific literature dealing with wildlife and the environment.[4,5] In September 1970, the National Swedish Environment Protection Board held a conference on PCBs.[6] One of the sessions of this conference highlighted the "environmental problem". This conference, perhaps for the first time, brought together the extent of understanding on the manufacture, use, and biological effects of, the extent of environmental contamination by, and the analytic methods for, PCBs.[6]

In August 1971, an Environmental Quality Workshop was convened in Durham, New Hampshire, by the National Academy of Sciences, to consider Marine Environmental Quality and Ocean Pollutants.[7] PCB contamination was highlighted.

In addition, provoked by both the accidental spills and by the widespread finding of trace quantities of PCBs in the environment, there emerged in the lay press a series of stories and articles dealing with PCB contamination. Most of them occurred in late 1971 and reflected especially the contamination of foodstuffs.[8-14]

The FDA, aware that PCBs were to be found as a contaminant in the environment, and alert to the occasionally reported cases of accidental spillages, elected to engage in watchful surveillance of food. It did this in part in cooperation with the Department of Agriculture. As a result of the findings of PCBs specifically in fish and milk, the FDA established, between December 1969 and February 1970, "Action Levels" for PCBs in milk, poultry and fish. Action levels are temporary thresholds for regulatory decision pending the establishment of a more permanent regulatory policy and procedure. In August 1970, the FDA established a similar action level for eggs. During 1970 and 1971, the FDA used these guideline values in various seizures of foods found contaminated with PCBs.

The number of reported contaminations of foods, recreational fish, packaging materials and animal feeds increased toward the latter half of 1971. Accompanying the announcements in the public press (and, undoubtedly, reflective of them), there also occurred toward the end of 1971 a series of inquiries from Congressmen and other elected officials over PCB contamination of food and the environment. On

[2] Jensen, S.: A new chemical hazard, New Scientist, *32*: 612 (1966).
[3] Widmark, G.: Possible interference by chlorinated biphenyls, J. Assoc. Offic. Anal. Chem., *50*: 1069 (1967).
[4] Peakall, D.B., and J.C. Lincer: Polychlorinated biphenyls. Another long-life widespread chemical in the environment, Bioscience, *20*: 958–964 (1970).
[5] Pichirallo, J.: PCBs: Leaks of toxic substance raises issues of effects, regulation. Science, *173*: 899–902 (1971).
[6] PCB Conference, National Swedish Environment Protection Board, Research Secretariat, Wenner-Gren Center, Stockholm, Sweden, 29 September 1970.
[7] Marine environmental quality, A special study held under the auspices of the National Scientific Committee on Oceanography of the National Academy of Sciences Ocean Affairs Board, Durham, New Hampshire, 9–13 August 1971.
[8] Monsanto limits food plants' use of chemical PCB, The Washington Post, 30 September 1971.
[9] Some dried foods found tainted by perilous chemical, The Washington Post, 28 September 1971.
[10] Tainted turkeys, The Washington Post, 24 September 1971.
[11] Turkeys, salmon tainted by PCBs, The Evening Star, 23 September 1971.
[12] A contaminant is found in cardboard, The New York Times, 28 September 1971.
[13] If you think DDT's a problem, meet PCB, The New York Times, 30 September 1971.
[14] FDA studying chance of contamination in containers for food, The Wall Street Journal, 28 September 1971.

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16 August 1971, Senator McGovern addressed a letter to the Commissioner of the FDA, reflecting this concern. In September, Governor Milliken of Michigan sent a telegram to Elliott Richardson, Secretary of HEW, in which he announced a restriction of commercial salmon fishing because of the finding of PCBs in fish.

By August 1971, the FDA (and to some extent, the USDA) found itself rapidly propelled into a position where it would be "required" by public pressure and advocacy to take a stronger and more forthright position against PCBs. The scientific issues were still not clear and there were glaring gaps in information. What really were the biological effects of the complex known as PCBs? How did the various PCBs vary in human toxicity and which members of the PCB family were found as contaminants? Was observed toxicity due to PCBs proper or to contaminants produced during their manufacture? How widespread was the contamination, and how good was the monitoring system in picking up accidental spills? Furthermore, it was clear that the twin issues of widespread environmental contamination, by trace quantities of PCBs, and the selective, higher level contamination of foods and feed, had to be joined at some point in Government decision-making.

On 5 August, 1971, the FDA, on its own initiative, called a meeting of spokesmen from each of several Government agencies and Federal research laboratories to review the state of scientific understanding of PCBs. The text for the meeting was the reported series of accidental spills and leakages.[15] Shortly following that meeting, the Department of Agriculture and the Commissioner of the FDA asked the Office of the President's Science Adviser to provide assistance and act as a focus for the Government's actions and decisions concerning PCBs. This request was made because: (1) the issue cut across several Federal agencies and also involved outside scientists, (2) the issue was rapidly becoming uncomfortable for the FDA to handle alone, and (3) the Office of Science and Technology already had under way a scientific review of polychlorinated biphenyls and had quietly begun to gather information several months back.

In April 1970, spokesmen for the Monsanto Company agreed to meet with the staff of the President's Science Adviser in the OST to discuss a number of issues concerning PCBs, including a series of animal toxicology studies which Monsanto had undertaken. During this meeting, Monsanto was asked for information concerning the amounts of PCB it manufactured and distributed. The company, being the sole producer in the U.S., was reluctant to make public this information, although it reported that it might be able to provide the data on a confidential, non-public, basis to the Government.

In October 1970, a review was begun, in the Office of Science and Technology, of the general subject of hazardous substances existing in the environment in trace quantities. This review, known ultimately as the Panel on Hazardous Trace Substances, had as its major goal the identification of the needs for information by the Government in making judgments about trace hazardous substances.

The Panel was composed principally of non-government experts in the fields of ecology, chemistry, biology, environmental and occupational medicine and geology. Three case studies were begun from which it was hoped to draw generalizable experience. The particular subjects for the case studies were chosen because they were thought to be of importance, because regulatory or other governmental action had not yet been taken but could be expected at some time in the reasonably near future, and because it was thought that there existed sufficient information from which to draw conclusions. The choices were cadmium, arsenic and PCBs.

Thus, as the Government began to develop its own position on PCBs in 1971, the OST-initiated study was already under way. What followed, in part, was for the Government to borrow the experience developed by the OST Panel and even for the two exercises to be joined to some extent. Notwithstanding, a separate and identifiable PCB report was published by the members of the Panel on Hazardous Trace Substances.[16]

On 1 September 1971, the FDA held a meeting with the USDA, the EPA, the Council on Environmental Quality, and the Office of Science and Technology, to explore options for further action concerning PCBs. The FDA and the USDA requested that the Office of Science and Technology take a lead role in handling this matter. OST acceeded to this request and agreed to collaborate with the CEQ in the task. This became known as the Interdepartmental Task Force on PCBs. The Task Force was announced on 5 September in a joint FDA-USDA press conference.[17]

On 15 September 1971, the OST Panel on Hazardous Trace Substances and the governmental Task Force met jointly with representatives of the Monsanto Company. The principal agenda item of this meeting was a request for information concerning the amounts of PCBs produced, patterns of distribution and usage, and estimates of losses into the environment.[18] Again, the manufacturers expressed their

[15] Transcript of proceedings of the interagency meeting on polychlorinated biphenyls (PCBs), Food and Drug Administration, Department of Health, Education, and Welfare, Washington, D.C., 5 August 1971.

[16] Polychlorinated biphenyls – environmental impact, A review by the panel on hazardous trace substances, March 1972. Environmental Research, 5: 249–362 (1972).

[17] Press release on interdepartmental PCB task force, Food and Drug Administration, Department of Health, Education, & Welfare, 5 September 1971.

[18] Letter from Edward J. Burger, Jr., M.D. of the OST to Mr. John Mason, The Monsanto Company, 15 October, 1971.

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willingness to supply information of this sort to the Government, but with the understanding that the data would not be released publicly except in a full and detailed fashion. In addition, the Monsanto Company expressed some concern over the seemingly disconnected character of the Government's activities up to that time and the difficulties involved in finding responsible spokesmen for each of the agencies involved. Monsanto made a strong plea (in the form of a condition for their supplying information) that they be permitted to deal with a single spokesman for the Government.

The office of Science and Technology, on the advice of the Counsellor to the President, did reach agreement with Monsanto on the terms of receiving the information.[19] These were shortly rendered moot by a request from the Environmental Defense Fund for the same information. This information ultimately served as important background for the Government's decisions and was leaned on heavily by both the OST Panel and the Task Force.

The OST Panel combined the production figures and the data on distribution and use with knowledge of the physical properties of PCBs to develop a composite picture of the rates and routes of environmental transport and disposition. The data were reflected in a series of coefficients for a model of transport of PCBs. While this was necessarily a crude description, it served as a very useful instrument for placing PCBs in perspective. It replaced what otherwise would have been a totally qualitative – even intuitive – exercise. It pointed up important gaps in knowledge. Finally, some verification was afforded by the results of physical measurement and monitoring. This attempt at environmental modelling was a major contribution by the Panel to decision-making.

The OST Panel report was also appropriately critical in its review of biological effects and analytic methods for PCBs. It considered what was known of the mechanisms of observed biological effects, and relationships between variations in chemical structure and biological activity, and it attempted to compare the effects of controlled laboratory experiments with observations made on animal populations in nature.

The Interdepartmental Task Force reflected much of this information in its report. It explored additional territory as well – reflective of the fact that it was a Government report which focused on a number of specific, pragmatic, governmental or public problems. Thus, as well as serving as a review of the scientific aspects of PCBs, the Task Force explicitly reviewed a number of broad aspects of the PCB question. Most important, perhaps, was the exploration of the benefits or utility of PCBs and of the industrial and commercial dependencies built up over the years. This explicit review of the benefits of PCBs, which is often not done for regulatory decisions, was of vital importance for decision-making on PCBs. The National Bureau of Standards engaged in a review and analysis of the benefits and even the "essentiality" of each of the several uses of PCBs. In this, the NBS received advice from the National Industrial Pollution Control Council, especially concerning the electrical uses of PCBs. In each of the cases examined, the question of a possible and satisfactory replacement for PCBs was raised. This review became the basis for the ultimate decision to preserve electrical uses of PCBs (for which there were true dependencies and no satisfactory substitutes) and to restrict other uses.[20]

The Government Task Force report included a systematic summary of monitoring experience for PCBs in food. It had been this matter of PCBs in food as much as any other which had brought PCBs to public notice. Hence, it was thought highly desirable to systematically lay out the apparent extent of food contamination and to consider what the patterns of contamination would suggest for public policy and Government action.

The Task Force Report explicitly reviewed all of the pertinent Federal regulatory laws for their applicability to PCBs. This was, therefore, an exploration of the power of the Government to control and limit the manufacture, distribution, use and disposal of PCBs. This review pointed out something that was already known – that existing regulatory authorities were capable of responding to specific incidents of contamination of foodstuffs once they were recognized. However, it acknowledged that the Government's legal armamentarium was generally "... inadequate to prevent more PCBs from entering the environment".[20]

In addition to the above, the Interdepartmental Task Force review considered the chemical and physical properties of PCBs, the occurrence, transfer and cycling of PCBs in the environment, and the known biological effects – especially on man.

During the time that the Government review of PCBs was being pursued, the level of public concern over these chemicals continued to rise considerably. For this reason, the Commissioner of the FDA felt compelled to hold a press conference to "... try to help establish a perspective on PCBs ..." roughly a month after the Task Force had begun its work.[21] This was an appropriately reasoned statement which attempted to allay fears and discourage demands for a sudden, outright ban on PCBs (even if

[19] Memorandum from John Dean, Counsellor to the President, to Edward J. Burger, Office of Science and Technology, concerning the Freedom of Information Act, 4 October 1971.

[20] Polychlorinated biphenyls and the environment. Interdepartmental task force on PCBs, Washington, D.C., May 1972. National Technical Information Service, U.S. Department of Commerce, Springfield, Virginia, No. COM-72-10419.

[21] Statement by Charles C. Edwards, M.D., PCB press briefing, Food and Drug Administration, 29 September 1971.

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the Government had been capable of invoking one). The statement deferred to the ongoing process of review and deliberation as the basis for considered decision and action.

There was, finally, a third review of PCBs undertaken within the Federal walls. One of the national institutes of health, the National Institute of Environmental Health Sciences, had sometime before elected to conduct a series of "scientific" reviews of materials which were of impending regulatory concern and for which no systematic accounting of scientific information had been done. The philosophy in this case was to bring together, in a conference, spokesmen for the principal research projects -- published or under way -- in order to take the measure of the available scientific understanding. At the same time, members of the press -- especially scientific writers -- were invited to attend these sessions, in order to enjoy the products of this review process. The aim was to educate both the scientists and the public.

In December 1971, the National Institute of Environmental Health Sciences held the first of this series of conferences in North Carolina, and it was on PCBs.[22] (Since then, the NIH has held similar reviews on lead, automotive emissions, and other substances of current public and governmental concern.) Many of the same spokesmen who were engaged in the other reviews made presentations at the "open" conference. One of the major accomplishments of this meeting was to impart an understanding to the press and science writers of the character of the scientific evidence and the scientists' own interpretation of experimental findings. The net (and immediate) effect of that exercise was to take the newsworthiness out of the PCB issue and to remove it from the category of the sensational. Very little was actually reported in the press of that meeting. More important, relatively little more was reported on PCBs in any form in the lay press.

The principal "control" actions for PCBs were the result of persuasion by the Federal Government rather than by direct regulatory exercise. The Government possessed no real regulatory authority to control the manufacture, distribution or use of PCBs. However, the persuasive influence of the several Government inquiries -- especially the PCB Interdepartmental Task Force -- was not doubted. Thus, the major action was taken "voluntarily" by the Monsanto Company, the sole U.S. manufacturer.

Beginning in 1970, the Monsanto Company had begun to reduce the sales of PCBs -- especially for non-electrical uses. Domestic sales for PCBs for non-electrical uses had risen from 12,000 tons in 1968 to 16,000 tons in 1970. By 1971, this figure was reduced to approximately 4,000 tons.[23] In addition, the Monsanto Company quietly assumed for itself the role of distributor as well as manufacturer in order to exercise some control over end-use of PCBs. In this way, the manufacturer was able to "discontinue sales of PCBs for use in paints, plasticizers, sealants, adhesives and other 'open-system' uses".

Thus, during 1971 and 1972, the Monsanto Company also restricted (or attempted to restrict) sales of PCBs to installations in which food or animal feed was processed.

The principal recommendation of the PCB Task Force was the discontinuance of all uses of PCBs except in electrical capacitors and transformers. These latter were judged to be essential uses and represented "closed systems".[24] To the extent that it could exercise this type of restriction on distribution, the Monsanto Company again undertook "voluntarily" to control end-use through its control of the manufacture and sale of PCBs.

OBJECTIVES

The Interdepartmental Task Force report on PCBs was issued publicly in May 1972 and was accompanied by a statement of governmental "thinking" and governmental "action". Perhaps the major conclusion reached in the report, which became an objective in Government decisions, was that of *limited* restriction on PCBs. PCBs were seen as having certain essential uses in electrical transformers and capacitors and it was judged in the country's best interest not to be totally denied the use of PCBs. This was a direct reflection of the analysis performed by the National Bureau of Standards of the utility and essentiality of PCBs, which pointed to the possibility of an increase in fires and explosions from encased or enclosed transformers if PCBs could no longer be used -- representing the possibility of trading one hazard for another hazard. In addition, it derived from the attempts to map out the patterns of environmental dispersal of PCBs which had been lost from human use. Electrical applications were seen as "closed" applications and were not thought to contribute to environmental distribution.

Other uses of PCBs were reviewed as either not essential, potentially or actually contributory to the environmental "load", or were found to have suitable substitutes. This, then, pointed to an elimination of

[22] National Institute of Environmental Health Sciences meeting on polychlorinated biphenyls (PCBs), Rougemount, North Carolina, 20-21 December 1971. Proceedings published in Environmental Health Perspectives, Experimental Issue No. 1, April 1972, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

[23] Monsanto Industrial Chemicals Company, press release: Monsanto releases PCB production figures to Department of Commerce, 30 November 1971.

[24] Press release accompanying the release of the PCB interdepartmental task force report on PCBs, Washington, D.C., 12 May 1972.

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essentially all other uses – heat exchange fluids, hydraulic fluids, and the miscellaneous category of "plasticizer" uses. The objective of limited restriction became the basis for governmental persuasion of the Monsanto Company to restrict its distribution and sales of PCBs – in fact, the principal governmental action.

Highlighting of the fact that true regulatory control by the Government was limited, became the text for a plea for passage of a then-pending bill in Congress to close this gap. A second objective, then, became the enactment of the Toxic Substances Control Act which would permit the Government to exercise useful control of industrial chemicals at their source.

The regulatory tools which the Government did possess in this case permitted enforcement action after PCBs were found in foods for human consumption and in animal feeds. Here, the FDA and the USDA re-stated their thresholds for action (which had been evolving over the previous four years), and announced the strengthening of their monitoring and analytic efforts. The other avenue of governmental control was that over industrial effluents and ambient water quality. Here, the Environmental Protection Agency stepped up its effort to assess the foreign chemical content of waters downstream from plants manufacturing PCBs and the Justice Department was close behind with enforcement teeth.

INFORMATION

The PCB "decisions" were perhaps among the best informed of governmental actions of this type in recent years. There was, it turned out, a certain body of scientific and technical knowledge about PCBs and a modest documentation of past experience. In addition, this information was better assembled and analyzed than was usually the case. Perhaps time was an important factor since time was permitted for deliberate and reasonably careful study and reflection before decisions were announced. Thirdly, there was more opportunity for public airing and scientific interpretation before decision-making than is usually the case. A Swedish scientific meeting on PCBs had been held in 1970.[6] The Office of Science and Technology had begun its review and analysis of PCBs by December 1970, and the results of its analysis were made available as they emerged. The Government's own scientists reviewed and interpreted the base of technical knowledge over roughly six months beginning in September 1971. In December 1971, a third forum of scientists was convened by the NIH to review much of the same material. Thus, the process of interpretation and maturation of data by scientific peers – while characteristic of the traditional scientific process but unusual in regulatory decision-making – was played out in this case.

The processes of review in this case explicitly sought information for a broadly-based decision. Thus, there was a dedicated attempt, for example, to determine the benefits or utility of PCBs and of the costs that could be expected if their uses were restricted or denied. This information was later found to have been highly influential and important in formulating the Government's position.

One other element of information which proved to be important was the analysis of environmental distribution and dispersal. The analysis itself was something of an experiment. It was reasoned early on by the participants in the OST review that it should be possible, starting with some elementary information on total amounts of PCBs produced, and patterns of distribution in commerce and disposal, and armed with a certain elementary understanding of physical and chemical properties, to build a model predicting PCB distribution in the environment. Thus, in fact, was done, and the coefficients used in the model were partially tested or "validated" against the physical measurements of PCBs in the environment which had been reported in the literature. This exercise and the information from it became the basis, for example, of the judgment that PCBs used in electrical capacitors disposed of in the earth by burying in landfills would not be expected to migrate very far through the soil and would not represent a significant source of environmental pollution.

IMPLEMENTATION

The principal "decisions" deriving from this exercise were to restrict PCBs to "closed-system" electrical uses. There soon emerged a few additional issues which reflected either loose ends or areas which deserve some additional study.

The principal reason for denying the use of PCBs as heat-exchange fluids was to avoid accidental spills and leakages of PCBs into foodstuffs (where heat was used to "pasteurize" the food material). However, there were often PCB heat exchanger applications. One of these, for example, involved the use of heat on off-shore oil rigs to maintain low viscosity of the oil. PCBs had been chosen here because of the characteristics of high thermal stability and low probability of fire and explosion, and many of the heat exchange devices had been designed specifically around the use of PCBs. Denial of the use of PCBs in this case raised the spectre of an increase in the number of fires in off-shore oil rigs or the continued use of PCBs from imported sources.

This general question of worldwide (as opposed to U.S.) production and use of PCBs, became a matter of immediate concern. There was an early visit of a spokesman from the Swedish Government to the Office of Science and Technology. The Tariff Com-

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mission and the Customs Bureau were pressed to search for signs of imported PCBs.[25] Perhaps most useful was the fact that the OECD was persuaded to take up the question of the industrial production and commercial use of PCBs in the industrialized parts of the world. PCBs, in fact, became the major example of intergovernmental "consultation" in a mechanism which the OECD had established for this purpose. The U.S. position and the information behind it became major elements in the OECD position paper[26] and in the deliberations at the OECD in November 1972.

Trace amounts of PCBs in packaging materials became a matter of particular concern. In part, this was due to uncertainty over their origin. There was some evidence that trace quantities of PCBs were magnified in the process of recycling paper. To the extent that this was true, the Government and national policies aimed at recycling were seen to be in possible jeopardy. One of the principal motives for exploring this particular issue, apart from the economics of paper and cardboard production, was the contamination of food wrapped with PCB-containing paper. There followed, therefore, a series of investigations by the Food and Drug Administration into the process and rate of migration of PCBs from packaging materials into foodstuffs which the packages contained. In December 1972, the FDA produced an Environmental Import Statement (perhaps the only one of its kind from that agency) on its proposed rule-making for PCBs.[27] Among other things, this document summarized the FDA investigations and positions regarding PCBs and packaging.

CONCLUSIONS, OBSERVATIONS, AND RECOMMENDATIONS

The Government "decisions" on PCBs constituted an unusual regulatory exercise compared to much of the experience of the past few years. In the first place, the Government's position was generally well prepared. Related to that was the fact that time was taken for deliberate study and deliberate action, even in the face of public outcries for immediate action. Thirdly, the "decisions" were taken without much tangible legal authority for governmental control. They represented, instead, persuasion and voluntary action. It is worthwhile, perhaps, to examine some of the factors which contributed to any successes that can be claimed.

1 The PCB decisions represented, perhaps, a somewhat more manageable challenge than many. Only a single U.S. manufacturer was involved. Further, the majority of commercial and industrial uses and the major users were known.

2 There was some information which proved useful in decision-making. Quantitative figures showing production were provided – albeit only after a delay – which were essential in determining the scale of the problem and its change with time. Similarly, the corresponding figures for commercial distribution were essential in ascertaining the patterns of human use and dispersion. To complement these data, there were at least some results of physical measurement and monitoring of PCBs in the environment or indices of dispersal.

In terms of hazards, there was a legacy of at least some documentation of previous human exposure and some laboratory data. However, many questions remained. Perhaps, most important, was the luxury of critical review (in fact, several critical reviews) of this information. Further, these reviews engaged some very good scientific talent – both inside and outside the Government and in a way which permitted the decision-makers to be very well informed of their advice.

In terms of benefits, a specific analysis was commissioned of the utility and essentiality of PCBs. (It is interesting to note that while this was done well, the National Bureau of Standards entered into this exercise very reluctantly, seeing in it the perils of the battery additive episode of some years before.)

Finally, there was performed the unusual but highly useful attempt at modeling the patterns of rates and routes of distribution of PCBs in the environment. This was done for the most part as an experiment to determine whether such an exercise could be performed. It did, in fact, provide some useful and immediate insight.

3 There was a single spokesman for the Government. The agencies involved early determined that the PCB question cut across several departments. This, by itself, was probably not persuasive and the joint request from the FDA and the USDA to the OST to "take on" the PCB question arose also from a desire on their part to push on to someone else a tough or "hot" decision. It should be noted, also, that the OST had already begun a review of PCBs.

The fact that there was a single spokesman

[25] Letter from Alvin Alm, Council on Environmental Quality, to Mr. Vernon Acree, Commissioner, Bureau of Customs, 22 June 1972.

[26] Organization for Economic Cooperation and Development, Environmental Directorate, Sector Group on Unintended Occurrence of Chemicals in the Environment, Polychlorinated biphenyls – proposals for concerted action, 13 October 1972.

[27] Food and Drug Administration, Final environmental impact statement. Rule making on polychlorinated biphenyls, Department of Health, Education, and Welfare, 18 December 1972.

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proved important in arriving at an orderly decision. The Monsanto Company insisted on dealing only with a single spokesman after months of unconnected and frustrating interchanges with a variety of Government agents. The fact that there was a single spokesman also undoubtedly made it easier to amass and analyze in an orderly fashion the variety of information from several sources. The fact that it was an Executive Office spokesman was probably important in soliciting certain other studies in parallel (such as the National Bureau of Standards' study of benefits) and the review of the Government-wide legal option for regulatory action.

4 Although already mentioned, the scientific information (especially that related to biological effects) underwent the benefit of several reviews. This had two salutary effects. It assured scientific interpretation by peers and it developed a constituency among scientists for the decisions ultimately taken.

5 The decisions were deliberately broadly-based. While this may appear elementary, this facet is generally not characteristic of regulatory decisions concerned with human health. Both benefits and hazards were explicitly explored. Economic consequences were considered. Each of several avenues of possible action was examined in turn. Again, a single spokesman for the Government and one placed above the operating agencies was probably a necessary feature in this broad examination.

6 The decision process was a relatively open one. The fact that there was an Interdepartmental Task Force was public knowledge from the outset. The Task Force published its full report. Similarly, the reports of the OST Panel on Hazardous Trace Substances and the report of the NIH meeting on PCBs were published. Further, science writers and other members of the press were specifically invited to participate in the NIH meeting. (Note that the question of freedom of information was a matter of some concern during the deliberations of the Interagency Task Force in the Office of Science and Technology.[19])

7 Time was permitted for deliberate decision-making. At one point, in fact, the Commissioner of the Food and Drug Administration held a press conference in which he specifically announced that he would not proceed with an outright ban on PCBs and deferred to the study process that was then underway.[24] This, of course, contradicts the classical argument which insists that Governments *must* make regulatory decisions immediately without the luxury of time for good decisions.

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PCB Enzymes

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A Comparative Study of Two Polychlorinated Biphenyl Mixtures (Aroclors 1242 and 1016) Containing 42% Chlorine on Induction of Hepatic Porphyria and Drug Metabolizing Enzymes[1]

JOYCE A. GOLDSTEIN, PATRICIA HICKMAN, VIRLYN W. BURSE[2] AND HENDA BERGMAN

Environmental Protection Agency, National Environmental Research Center, Research Triangle Park, North Carolina 27711

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A Comparative Study of Two Polychlorinated Biphenyl Mixtures (Aroclors 1242 and 1016) Containing 42% Chlorine on Induction of Hepatic Porphyria and Drug-Metabolizing Enzymes. GOLDSTEIN, J. A., HICKMAN, P., BURSE, V. W. AND BERGMAN, H. (1975) *Toxicol. Appl. Pharmacol.* **32**, 461–473. Aroclor 1242 and Aroclor 1016 are polychlorinated biphenyl (PCB) mixtures with similar chlorine content (42 vs 41%), but Aroclor 1242 contains 9% biphenyl homologs with five or more chlorines while Aroclor 1016 contains only 1%. The effects of Aroclor 1242 and Aroclor 1016 on induction of hepatic porphyria and drug-metabolizing enzymes were compared in female rats fed 100 ppm or 500 ppm of each. At 1 wk, Aroclor 1242 markedly increased liver weight and all drug-metabolizing pathways tested including cytochrome P-450, liver weight, *N*-demethylase, nitroreductase, aniline hydroxylase, and glucuronyl transferase, while Aroclor 1016 had produced only very minimal effects. At 6 mo, however, 500 ppm of either Aroclor markedly increased drug-metabolism, while at the lower dose, Aroclor 1016 was much less effective than Aroclor 1242. Both doses of Aroclor 1242 produced porphyria, but only the higher dose of Aroclor 1016 was porphyrogenic. The porphyria occurred after a lag of 6 mo and was characterized by excretion and hepatic storage of uroporphyrins. Aroclor tissue concentrations were similar in rats fed equal doses of the two mixtures. Therefore, the marked differences in the biological effects of Aroclor 1016 and Aroclor 1242 cannot be explained by differences in absorption, metabolism, or excretion.

Polychlorinated biphenyls (PCBs) are industrial chemicals which have been widely used and are widespread contaminants of the environment (Risebrough *et al.*, 1968). In the United States, PCBs are sold under the trademark Aroclor. They are mixtures containing various percentages of organically bound chlorine by weight. PCBs have been found in human tissue and were responsible for an outbreak of chloracne in

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[2] Present address: Consumer Products Safety Commission, 1330 W. Peachtree NW, Atlanta, Ga. 30309.

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Japan (Yobbs, 1972; Kuratsune *et al.*, 1972). Chronic exposure to PCBs results in porphyria resembling hexachlorobenzene poisoning, characterized by delayed onset and massive increases in urinary and liver uroporphyrins (Goldstein *et al.*, 1974a). PCBs are also known to induce the activity of the hepatic mixed-function oxidase system which metabolizes foreign chemical and endogenous steroids (Litterst *et al.*, 1972). These authors reported that effects on the microsomal mixed function oxidase system correlated directly with the percent chlorine. It has been reported that biphenyls with higher numbers of chlorine per molecule are retained in tissues for longer periods of time, while biphenyls with fewer numbers of chlorines appear to be preferentially metabolized and excreted (Weigel and Smith, 1974; Curley *et al.*, 1971). Preferential retention of highly chlorinated biphenyls could explain the greater biological effectiveness of highly chlorinated PCB mixtures compared with mixtures with lower percent chlorination.

At present, sale of American-made PCBs is limited largely to uses as dielectric fluids in capacitors and transformers. Currently, the major PCB mixture being marketed in the United States is Aroclor 1016, a mixture containing 41.3% chlorine with a very low percentage (1%) of biphenyls with more than four chlorines per molecule. Only one study on the biological effects of Aroclor 1016 has been published. This study compared the effects of Aroclor 1016 with Aroclor 1254 (a biphenyl mixture containing 54% chlorine) on certain pathways of drug metabolism (cytochrome P-450, ethylmorphine *N*-demethylase, aniline hydroxylase, zoxazolamine, and hexobarbital metabolism) after administration to rats of 25 mg/kg day for 6 days (Bickers *et al.*, 1972). Aroclor 1254 produced up to a 3-fold increase in some drug-metabolizing enzymes, while the maximum increase produced by Aroclor 1016 was 40%. Effects of chronic administration of Aroclor 1016 were not determined. Litterst *et al.* (1972) reported up to threefold increases in nitroreduction of *p*-nitrobenzoic acid and hydroxylation of pentobarbital by Aroclor 1242, a mixture containing approximately 42% chlorine. Because of the reports that, in general, biphenyls with greater numbers of chlorines are excreted, it appeared possible that the lesser effects of Aroclor 1016 could be due to greater metabolism and/or excretion because of its very low content of highly chlorinated biphenyls. In addition, it was not known whether Aroclor 1016 or Aroclor 1242 were less porphyrinogenic than other Aroclor mixtures. Therefore, the present study was undertaken to compare the effects of Aroclor 1016 with another chlorinated biphenyl mixture, Aroclor 1242 (with similar chlorine content (42%) but containing 9% biphenyls with five or more chlorines vs 1% for Aroclor 1016). Effects of two relatively high doses of Aroclor 1016 and Aroclor 1242 were compared at both 1 wk and 6 mo on a large variety of drug-metabolizing pathways as well as porphyrin accumulation and excretion. In addition, total PCB content of liver and fat were compared after administration of comparable doses of the two compounds.

METHODS

Thirty 1-mo old female Sherman rats were divided into five groups of six each and fed pronto Purina laboratory chow *ad libitum* containing 100 or 500 ppm Aroclor 1016 (lot No. KB-06-756) (Monsanto Chemical Co., St. Louis, Mo.), or plain chow. Rats were sacrificed by decapitation after 1 wk. An additional 30 rats were treated in a

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similar fashion and sacrificed at 6 mo. Urine was collected in metabolic cages for the 24-hr period preceding sacrifice.

After sacrifice, liver homogenates, 9000 *g* supernates and microsomes were prepared as previously described (Goldstein *et al*., 1974a). δ-Aminolevulinic acid (ALA) synthetase was assayed in whole liver homogenates (Marver *et al*., 1966a). *o*-Aminophenol glucuronyl transferase was assayed in microsomes equivalent to 50 mg wet wt of liver (resuspended in 1.15% KCl) in the presence of 0.3% digitonin and 2.7 mol/ml of UDPGA (Goldstein and Tarnog, 1968). Aminopyrine *N*-demethylase, aniline hydroxylase, and nitroreductase were assayed in 9000 *g* supernates (Goldstein *et al*., 1973b). Aniline hydroxylase was assayed in the dark. *N*-demethylase was measured by determination of formaldehyde produced (Cochin and Axelrod, 1959), and aniline hydroxylase by determination of *p*-aminobenzoic acid from *p*-nitrobenzoic acid (Louis and Brodie, 1957) with the following modification.

Porphyrin in liver fractions from porphyric rats interfered with analysis of products of drug metabolizing enzymes by producing high blanks. In addition, porphyrins interfered specifically with analysis of *p*-aminophenol which is coupled with phenol in alkaline solution to form an indophenol dye and measured spectrophotometrically (Kato and Gillette, 1965). The reaction product was unstable in the presence of porphyric tissue, disappearing variably during the reaction period. Therefore, we routinely removed porphyrin from all protein-free supernatant fractions of drug-metabolizing reactions by the addition of 50 mg/ml tale to the incubation mixtures after the reactions were stopped with acid. The tale, which adsorbed the porphyrins in acid conditions, was precipitated by centrifugation at 2000 *g* for 15 min, and the porphyrin-free supernates were analyzed for *p*-aminophenol, formaldehyde, *p*-aminobenzoic acid, or *o*-aminophenol glucuronide as described above. Recoveries of all compounds were unaffected by tale.

Microsomal cytochrome P-450 and protoheme were determined by the methods of Omura and Sato (1964a, b) using an Aminco DW-2 spectrophotometer. Microsomal protein (Lowry *et al*., 1951), tissue porphyrins (Doss, 1967), urinary porphyrins (Goldstein *et al*., 1974a), and urinary ALA and porphobilinogen (PBG) (Marver *et al*., 1966b) were measured as previously described. Tissue residues of PCBs were analyzed by gas chromatography (GC) using a Micro Tek MT-220 and quantitated by comparing the sum of the peak heights with the sum of total peak heights in the corresponding Aroclor standard (Curley *et al*., 1971).

Results were analyzed by analysis of variance followed by Duncan's multiple range test (Steel and Torrie, 1960).

RESULTS

At 500 ppm, 500 ppm of Aroclor 1242 markedly increased cytochrome P-450 (4-fold), *N*-demethylase (2.5-fold), aniline hydroxylase (6.8-fold), nitroreductase (3-fold), glucuronyl transferase (4-fold), and microsomal protoheme (2.6-fold), and produced moderate increases in ALA synthetase (36%) and liver weight (28%) (Fig. 1). In contrast, 500 ppm Aroclor 1016 produced only a 50% increase in most enzymes. Effects of 500 ppm Aroclor 1016 were significantly lower than those of 500 ppm Aroclor 1242 on all parameters except nitroreductase. The smaller dose of 100 ppm Aroclor 1242

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caused significant increases in cytochrome P-450, (2-fold), aniline hydroxylase (2.5-fold), glucuronyl transferase (2-fold), ALA synthetase (122%), microsomal protoheme (60%) and liver weight (9%); while 100 ppm Aroclor 1016 had no effects. The peak of the CO-difference spectrum of cytochrome P-450 was shifted from 450 to 449 nm by Aroclor 1242 treatment but not by Aroclor 1016.

At 6 mo, 500 ppm Aroclor 1242 had lesser effects on cytochrome P-450 and *N*-demethylase than at 1 wk, but aniline hydroxylase, nitroreductase, and liver weight

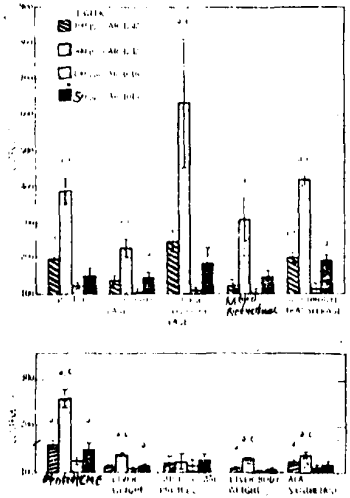

FIG. 1. Effect of Aroclors 1016 and 1242 on cytochrome P-450, drug metabolizing enzymes, protoheme, liver weight, liver microsomal protein, and ALA synthetase activity at 1 wk. Groups of six female rats were fed 100 or 500 ppm of Aroclors 1016 or 1242 and sacrificed at 1 wk. Values represent means ± SE. a: Significantly greater than controls at $p < 0.05$. b: 100 ppm Aroclor 1242 significantly greater than 100 ppm Aroclor 1016, $p < 0.05$. c: 500 ppm Aroclor 1242 significantly greater than 500 ppm Aroclor 1016, $p < 0.05$.

remained elevated (Fig. 2 vs Fig. 1). In contrast, the effects of Aroclor 1242 on glucuronyl transferase (1.3-fold vs 4-fold) and ALA synthetase (5- to 9-fold vs 1.3-fold) were much greater at 6 mo than at 1 wk. In addition, the effects of 500 ppm of Aroclors 1016 and 1242 were roughly comparable at 6 mo; 500 ppm Aroclor 1016 caused marked increases in glucuronyl transferase (11-fold), ALA synthetase (7-fold), nitro-

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reductase (2-fold), aniline hydroxylase (2-fold), and liver weight (29%) (Fig. 2). However, the effects of 500 ppm Aroclor 1016 were significantly lower than the effects of 500 ppm Aroclor 1242 on aniline hydroxylase, nitroreductase, and glucuronyl transferase. At the low dose of 100 ppm, Aroclor 1016 had relatively slight effects, in

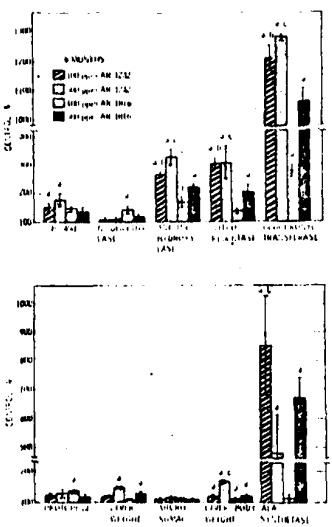

FIG. 2. Effect of Aroclors 1016 and 1242 on cytochrome P-450, drug-metabolizing enzymes, protoporphyrin, liver weight, liver microsomal protein, and ALA synthetase activity at 6 mo. Groups of six female rats fed 100 or 500 ppm of Aroclors 1016 and 1242 were sacrificed at 6 mo. Values represent means ± SE. a: Significantly greater than controls at $p < 0.05$. b: 100 ppm Aroclor 1242 significantly greater than 100 ppm Aroclor 1016, $p < 0.05$. c: 500 ppm Aroclor 1242 significantly greater than 500 ppm Aroclor 1016, $p < 0.05$.

contrast to the marked effects of Aroclor 1242. These differences were statistically significant for aniline hydroxylase, nitroreductase, glucuronyl transferase, and ALA synthetase.

Weight gain was significantly decreased only by the high dose of Aroclor 1242 at 6 mo (151 ± 11 vs 196 ± 7 g). At 6 mo, the dose of Aroclor consumed was 6 mg/kg/day for rats fed 100 ppm Aroclor 1242 or 1016 and 30 mg/kg/day for rats fed 500 ppm

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Aroclor 1242 or 1016. The uterine horns of most rats on both doses of Aroclors 1016 and 1242 were swollen at 1 wk and markedly swollen at 6 mo.

Porphyria

At 1 wk, neither Aroclor 1016 or Aroclor 1242 had any effects on liver or urinary porphyrins or PBG (Figs. 3 and 4) (Table 1). A small increase in urinary ALA was seen in rats fed 500 ppm Aroclor 1242, but the significance of this increase is questionable. At 6 mo, however, both doses of Aroclor 1242 and 500 ppm 1016 produced large increases in hepatic porphyrins (1000-fold) (Table 1) and urinary uroporphyrins (200-fold) (Fig. 4) and moderate increases in coproporphyrin (8-fold), urinary ALA and PBG (approx. 3- and 10-fold) (Fig. 3). The porphyrin found in the livers of

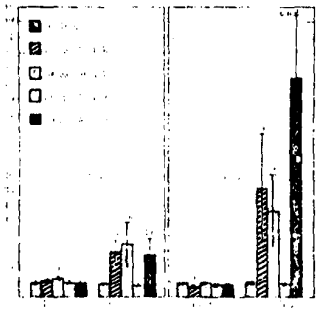

FIG. 3. Effects of Aroclors 1016 and 1242 on urinary ALA and PBG. Rats were treated as described in Figs. 1 and 2, and urine was collected in individual metabolic cages for 24 hr preceding sacrifice. Values represent means + SE. The numbers above the bars represent the proportion of animals whose individual values were outside the 99% confidence limits of the controls at $p < 0.01$. a = Significantly different from controls, $p < 0.05$.

PCB-treated rats was identified as 8- and 7-carboxyporphyrins. None of the rats fed 100 ppm Aroclor 1016 showed any evidence of increased liver or urinary porphyrins. Analysis of urinary ALA, PBG, and porphyrins at 12 days, 2 mo, 4 mo, and 6 mo showed that porphyrinuria occurred after 2–6 mo. There was no clear indication of a different time course in the development of porphyria in Aroclor 1242 vs Aroclor 1016 treated rats.

Tissue PCB Content

Comparing the GC profile of tissue PCBs from Aroclor 1242 and Aroclor 1016 fed animals with the GC profile of the appropriate Aroclor standard, we found disappearance of a number of peaks, changes in the ratios of the peaks, and possible emergence

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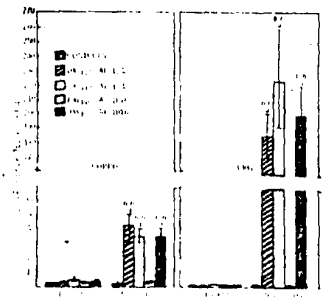

FIG. 4. Effects of Aroclors 1016 and 1242 on urinary coproporphyrin and uroporphyrin excretion. Treatment is described in Fig. 3. Values represent means ± SE. The numbers above the bars represent the proportion of animals whose individual values were outside the 99% confidence limits of the controls at $p < 0.01$. a Significantly different from controls, $p < 0.01$.

TABLE 1

EFFECT OF AROCLORS 1016 AND 1242 ON LIVER PORPHYRINS IN THE RAT[a]

Treatment	1 Week		6 Months	
	7-COOH	8-COOH	7-COOH	8-COOH
Control	Trace[b]	Trace[b]	Trace[b]	Trace[b]
100 ppm Aroclor 1242	Trace[b]	Trace[b]	164 ± 27	534 ± 61
500 ppm Aroclor 1242	Trace[b]	Trace[b]	227 ± 59	669 ± 146
100 ppm Aroclor 1016	Trace[b]	Trace[b]	Trace[b]	Trace[b]
500 ppm Aroclor 1016	Trace[b]	Trace[b]	89 ± 23	343 ± 65

[a] Porphyrins were methylated and analyzed by thin-layer chromatography. Female rats were treated as described in Fig. 1. Results are given as the mean ± SE.
[b] < 1 μg/g.

of additional late-eluting peaks (Figs. 5 and 6). The GC residue profiles of all three tissues from Aroclor 1242 fed rats contained 11 major peaks, while those from Aroclor 1016 fed rats contained five major peaks. The total PCB content was similar in liver and fat of animals fed comparable doses of Aroclor 1242 or Aroclor 1016 (Fig. 7). In particular, rats fed 100 ppm of either Aroclor for 6 mo had comparable liver, blood, and fat PCB concentrations despite markedly different biological effects. At the high dose of 500 ppm, the PCB content of livers from rats fed Aroclor 1242 for 1 wk was significantly higher than liver PCB residues in rats fed Aroclor 1016; however, fat content was comparable.

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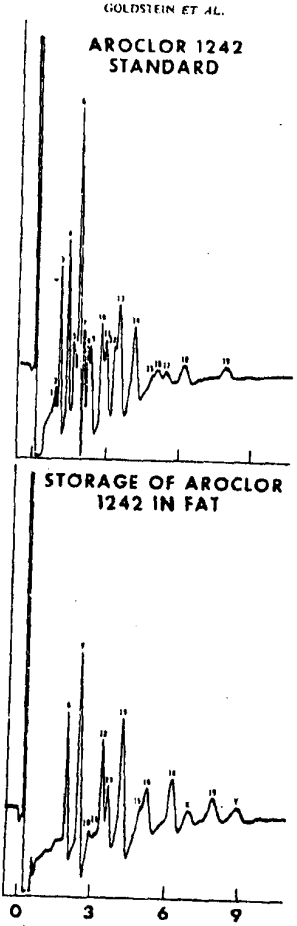

FIG. 5. Gas chromatographic profile of Aroclor 1242 standard and residue from fat of rats fed 100 ppm Aroclor 1242 for 6 mo. Peaks were numbered consecutively according to retention time. Two peaks (labeled A and B) were found in extracts of tissues from Aroclor 1242-fed animals but not in the Aroclor 1242 standard.

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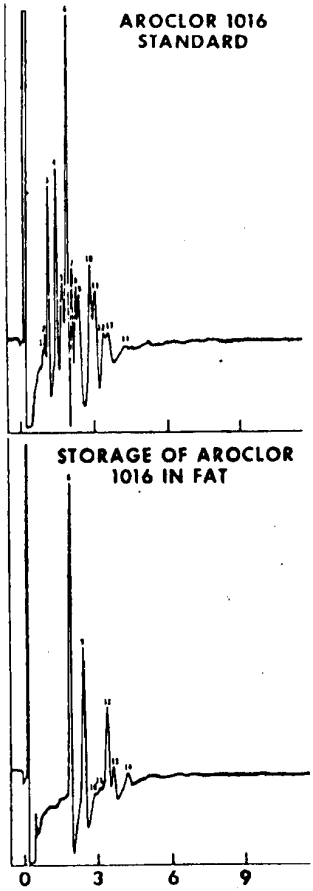

FIG. 6. Gas chromatographic profile of Aroclor 1016 standard and residue from fat of rats fed 100 ppm Aroclor 1016 for 6 mo. Peaks were numbered consecutively according to retention time.

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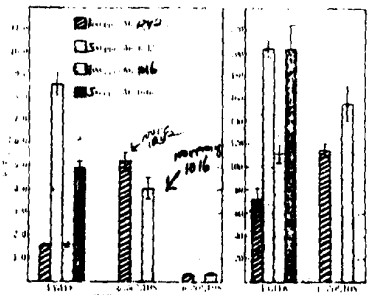

FIG. 7. Tissue PCB content of female rats fed Aroclor 1016 or 1242. Rats were treated as in Fig. 1. Values represent means ± SE. a = 500 ppm Aroclor 1016 significantly different from 500 ppm Aroclor 1242. b = 100 ppm Aroclor 1016 significantly different from 500 ppm Aroclor 1242.

DISCUSSION

We show that Aroclor 1242 markedly increases liver weight, cytochrome P-450, *N*-demethylase, aniline hydroxylase, nitroreductase, and glucuronyl transferase activity when fed to female rats for 1 wk, while Aroclor 1016 has only very slight effects on liver drug-metabolizing enzymes and no effect on liver weight. Bickers *et al.* (1972) similarly found only 30% increases in cytochrome P-450 and ethylmorphine *N*-demethylase and no increases in liver weight after six daily doses of Aroclor 1016 (25 mg kg/day). However, he compared Aroclor 1016 with Aroclor 1254, a mixture with higher chlorine content, and concluded that the lesser effects of Aroclor 1016 probably related to the lower chlorine content. Similarly, Litterst *et al.* (1972) showed that the potency of PCB mixtures as inducers of drug-metabolizing enzymes increased with increasing percentage of chlorination. We show that Aroclor 1016 is much less effective than Aroclor 1242, despite similar chlorine content. Therefore, the ability of PCBs to induce drug-metabolizing enzymes does not depend simply on percentage of chlorination. Aroclor 1242 may be a more potent inducer than Aroclor 1016 because it contains a higher concentration of penta- and hexachlorobiphenyls, which may be the most active inducers in the mixture.

In contrast to its minimal effects at 1 wk, 500 ppm Aroclor 1016 markedly increased glucuronyl transferase, aniline hydroxylase and nitroreductase activity as well as liver weight and caused porphyria at 6 mo. These results were completely unexpected in view of the earlier study of Bickers *et al.* (1972) which reported minimal effects of Aroclor 1016 on drug metabolism and liver weight, apparently because they studied only a 6 day dosage period. The present study demonstrates that the effects of chronic exposure cannot be predicted by short-term dosage. In particular, the porphyria produced by Aroclor 1016 could not have been predicted on the basis of short-term studies. The effects of Aroclor 1242 also differed with length of administration. Some

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effects were less noticeable at 6 mo than at 1 wk; other pathways were increased comparably or even more markedly after long-term administration. We have previously noted that effects of piperonyl butoxide on glucuronyl transferase were much more pronounced after 2 mo, while most other drug-metabolizing enzymes were maximally increased after 1 wk (Goldstein *et al.*, 1973b).

Aroclor 1242 shifted the maximum of the CO-difference spectrum from 450 to 449 nm, but Aroclor 1016 had no discernable effect, possibly because Aroclor 1016 increased cytochrome P-450 content only minimally. A similar shift of the CO-difference spectrum and an increase in the 455:430 ratio of the peaks of the ethyl isocyanide difference spectrum has been noted after Aroclor 1254 administration (Alvares *et al.*, 1973). These changes are similar to those produced by polycyclic hydrocarbons; however, PCBs, unlike polycyclic hydrocarbons, stimulate a variety of pathways.

Both Aroclors 1016 and 1242 produced swelling of the uterine horns. DDT and PCBs with less than 54% chlorination have been reported to have estrogenic effects on the rat uterus (Bitman and Cecil, 1970). Aroclor 1016 appears at least as effective as Aroclor 1242 in the present study. At present, no studies of the effects of Aroclor 1016 on reproduction have been reported.

Previously, we showed that 100 ppm Aroclor 1254 increased urinary excretion and hepatic accumulation of uroporphyrins and induced ALA synthetase, the rate-limiting step in heme synthesis, after a lag of several months (Goldstein *et al.*, 1974a). Both 100 ppm and 500 ppm Aroclor 1242 produced similar effects after 6 mo, while only the high dose of Aroclor 1016 was effective. Apparently, the lag in development of PCB-induced porphyria did not depend on greater tissue accumulation of PCBs with time, since rats fed 100 ppm Aroclor 1242 for 6 mo were porphyric, while rats fed 500 ppm Aroclor 1242 were not porphyric at 1 wk despite higher tissue PCB levels. A similar unexplained lag has been observed in hexachlorobenzene-induced porphyria (Ockner and Schmid, 1961), in contrast to porphyrogenic drugs such as allylisopropylacetamide which increase excretion of porphyrins and their precursors within hours (De Matteis and Prior, 1962).

The lesser effects of Aroclor 1016 than 1242 could not be explained by greater metabolism and excretion, since tissue concentrations were comparable. Other workers in our laboratory found plasma, kidney, brain, liver, and fat content of PCBs were generally higher in rats fed 100 ppm Aroclor 1016 than in rats fed Aroclor 1242 for 0.5, 1, 2, 4, 6, 8, or 10 mo (Morse *et al.*, 1974). It is probable that induction of liver enzymes and hepatic porphyria by PCBs depends on both the number and position of chlorine atoms on the PCB molecule. Significantly, Bush *et al.* (1974) found high correlation between occupation of the 4,4' positions, tissue retention, cytochrome P-450, and aniline hydroxylase activity after administration of Aroclor 1254. Compounds with one or both *p*-positions open were not persistent in tissue.

Two European commercial preparations of PCBs have been reported to be contaminated with 5–20 ppm of 2,3,7,8-tetrachlorodibenzofuran (TCDF) (Vos *et al.*, 1970). The related compound, 2,3,7,8-tetrachlorodibenzodioxin (TCDD), induces ALA synthetase in the chick embryo at doses as low as 0.5 μg/kg (Poland and Glover, 1973), induces hepatic porphyria in the mouse at doses of 100 μg/kg (Goldstein *et al.*, 1973a), and increases hepatic cytochrome P-450, glucuronyl transferase, and a number of drug-metabolizing enzymes at doses as low as 1 μg/kg (Lucier *et al.*, 1973). Vos

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et al. (1970) could not detect TCDF in American-made PCBs at a sensitivity limit of 1 ppm, but Curley *et al.* (1972) reported contamination of Aroclor 1254 with a trace of TCDF (less than 1 ppm). TCDD was not detected. It is doubtful whether contamination of Aroclors with less than 1 ppm TCDF could attribute appreciably to the hepatic effects of PCBs, since a number of synthetically prepared hexachlorobiphenyls induce ALA synthetase, cytochrome P-450, glucuronyl transferase, and porphyria in the chick, while TCDF does not induce porphyria, even at lethal doses, has little effect on cytochrome P-450, and no effect on glucuronyl transferase or ALA synthetase (Goldstein *et al.*, 1974b). Similarly, TCDF did not induce porphyria in the mouse at 40-times the porphyrogenic dose of TCDD under identical conditions (Goldstein *et al.*, 1974b). Therefore, it is probable that differences in the effects of various PCB mixtures on the liver are due to the effectiveness of the various chlorinated biphenyl homologs in each mixture. Aroclor 1016 is less potent in its effects on the liver, probably because it contains fewer of the biphenyls which are the most active inducers of liver drug-metabolizing enzymes.

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