

RESEARCH ARTICLE

‘In the absence of adequate data on humans’: animal bioassay and the transnational machinery for controlling carcinogens

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Abstract

From the 1960s onwards, a growing number of national and international organizations began working to define more precisely what constitutes a carcinogenic exposure. The central question for these new groups of experts soon became what kinds of data authorities should rely on to govern chemicals and their uses. Drawing on new archival material from the World Health Organization’s International Agency for Research on Cancer, this paper examines the dramatic rise and contested decline of the animal bioassay for carcinogenicity in this domain. The legitimation of this type of study was inseparable from the very emergence of the institutional machinery responsible for controlling carcinogens. During the 1970s and 1980s, establishing the animal bioassay as evidence of carcinogenicity became a way for scientific and regulatory institutions to stabilize relations among themselves. But what had been done could also be undone. The validity of animal studies was challenged on the ground of possible high-dose artefacts in rodents, as well as on that of the emergence of new cellular tests promising to be quicker, cheaper and more precise. These criticisms destabilized the institutional order linked to the animal bioassay standard, even as actors managed to contain the threat – allowing these studies to remain at the core of the field.

For many of the chemicals evaluated ... for which there is sufficient evidence of carcinogenicity in animals, data relating to carcinogenicity for humans are either insufficient or nonexistent. In the absence of adequate data on humans, it is reasonable, for practical purpose, to regard such chemicals as if they were carcinogenic for humans.

IARC Monographs (1978) 18, p. 22

This statement was published at the end of the 1970s by the International Agency for Research on Cancer (IARC), an agency of the World Health Organization with relatively little media coverage. It appears in a scientific document in a series that is not very accessible to the public, the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. However, what it states is, even today, of capital importance for cancer prevention policies and control of markets in chemical substances. Most pesticides and other workplace or environmental chemicals classified or regulated for their carcinogenicity have been

initially identified either solely on the basis of animal studies or through a combination of animal evidence and weaker human data. Glyphosate, the widely used flame retardant tetrabromobisphenol A, certain poly- and perfluoroalkyl substances (PFAS), and certain phthalates are among the more recent examples. This weight given to animal studies has underpinned the decisions of a range of public-health expert groups and, consequently, those of a range of political authorities in Europe and North America. The historical perspective is essential to understand this state of affairs, and not to take it as the logical consequence of a self-evident scientific consensus.¹ For animal data to prevail within this transnational institutional complex, it was necessary for a number of actors to work toward making them indispensable elements in the functioning of various health expertise institutions. This work eventually encountered resistance, and the value of animal studies was challenged almost as soon as it had been consolidated. Interestingly, these contestations threatened the legitimacy of these institutions and the networks of interdependence connecting them. This paper addresses this historical process from the 1970s to the 2010s. It looks at the construction, adoption, diffusion and contestation at a transnational scale of the specific regulatory norm establishing the equivalence between animal and human evidence. I argue that the legitimization of animal bioassay was inseparable from the very emergence of the institutional machinery responsible for controlling carcinogens. During the 1970s and 1980s, establishing this type of study as evidence of carcinogenicity became a way for scientific and regulatory institutions to stabilize relations among themselves and to determine how much weight should be given to their respective forms of expertise. In other words, studying the historical development of regulatory standards also means studying the formation of institutions in the classical sense of the term – that is, the established practices, prevailing views and formal rules that create predictability and order by reducing uncertainty.² In this case, this predictability and order concern what should or should not be considered a carcinogen.

The IARC's assertion mentioned in the epigraph is part of a broader production of norms, which the social sciences have termed 'regulatory science' and identified as being produced within a network of institutions by a bureaucracy sometimes described as 'technical'.³ Based on the state of scientific knowledge, these standards are intended to produce expertise for political authorities. Two lines of analysis can be drawn from the existing literature. The first focuses on the boundary work between science and politics that is at the core of these standards.⁴ Indeed, regulatory science puts in tension the ever-debated and evolving

¹ Valentin Thomas, 'Deadly hazard without risk? How toxic exposure has been downplayed in transnational conflicts over carcinogen assessment', *Comparativ* (2025) 35(3), pp. 315–37; Thomas, *Classé cancérigène: Enquête sur un processus entravé*, Paris: Presses de Sciences Po, 2025.

² Peter Hall and Rosemary Taylor, 'Political science and the three new institutionalisms', *Political Studies* (1996) 44, pp. 936–57; Walter W. Powell and Paul J. DiMaggio (eds.), *The New Institutionalism in Organizational Analysis*, Chicago: University of Chicago Press, 1991, pp. 1–39.

³ Daniel Benamouzig and Julien Besançon, 'Administrer un monde incertain: Les nouvelles bureaucraties techniques. Le cas des agences sanitaires en France', *Sociologie du travail* (2005) 3(47), pp. 301–22; David Demortain, *The Science of Bureaucracy: Risk Decision-Making and the US Environmental Protection Agency*, Cambridge, MA: MIT Press, 2020; Demortain, 'Expertise, regulatory science and the evaluation of technology and risk: introduction to the special issue', *Minerva* (2017) 2(55), pp. 139–59; Evan Hepler-Smith, 'Molecular bureaucracy: toxicological information and environmental protection', *Environmental History* (2019) 24(3), pp. 534–60.

⁴ Ronald Brickman, Sheila Jasanoff and Thomas L. Ilgen, *Controlling Chemicals: The Politics of Regulation in Europe and the United States*, Ithaca, NY: Cornell University Press, 1985; Jean-Paul Gaudillière and Pierre-Benoît Joly, 'Appropriation et régulation des innovations biotechnologiques: Pour une comparaison transatlantique', *Sociologie du travail* (2006) 3(48), pp. 330–49; Sheila Jasanoff, *The Fifth Branch: Science Advisers as Policymakers*, Cambridge, MA: Harvard University Press, 1990; Mark E. Rushefsky, *Making Cancer Policy*, Albany: State University of New York Press, 1986.

nature of scientific knowledge on the one hand, and the need for certainty and stable criteria over time on the part of political authorities on the other.⁵ A second and more recent body of work questions the political and economic interests promoted by these norms. This research may combine theoretical approaches or mobilize various notions to capture the presence of business forces in expert committees.⁶ A range of authors have focused on the notion of the ‘production of ignorance’ to understand the interplay between the interests of the actors behind regulatory standards and the effects in terms of knowledge and control of health risks.⁷ Beyond their differences, these two bodies of work are similar in at least two respects. First, they question these norms from the point of view of the trade-offs that regulatory organizations manage between the different groups of actors (i.e. administrators versus scientists, or public and occupational health advocates versus industry), and the different strategies for influencing these trade-offs. Depending on the circumstances, defining legitimate animal data in a certain way, or giving them more weight, for example, has been seen either as a way to favour the interests of employers or, on the contrary, as a way to favour the interests of workers or consumers exposed to certain products.⁸ Several authors have addressed the way animal bioassay fostered chemical bans or public-health policies, as well as the way it has been challenged by certain scientists or private economic actors supporting new kinds of short-term test, presented as cheaper and faster to produce.⁹

My argument builds on this body of research, but moves from this debate about whether the organizations that constitute the national or transnational regulatory machinery are or are not driven by social forces defending public health, business interests, politics or science. Indeed, these organizations are not only conflictual interfaces between different external actors. They also have their own logic and institutional interests. I argue that by adopting, rejecting or negotiating these norms, these institutions negotiate their own position in the regulatory field.

Second, the expert groups that develop these standards are most often studied separately, organization by organization. Yet, as shown by existing work, these national and

⁵ Scott Frickel, *Chemical Consequences: Environmental Mutagens, Scientist Activism, and the Rise of Genetic Toxicology*, New Brunswick, NJ: Rutgers University Press, 2004; Sara Shostak, *Exposed Science: Genes, the Environment, and the Politics of Population Health*, Berkeley: University of California Press, 2013.

⁶ David P. McCaffrey, *OSHA and the Politics of Health Regulation*, New York: Springer, 2013; Boris Hauray, ‘Introduction. Conflits d’intérêts et santé publique: L’apport des sciences sociales’, *Sciences sociales et sante* (2020) 3(38), 2020, pp. 5–19.

⁷ Henri Boullier, *Toxiques légaux: Comment les firmes chimiques ont mis la main sur le contrôle de leurs produits*, Paris: La Découverte, 2019; Scott Frickel and M. Bess Vincent, ‘Hurricane Katrina, contamination, and the unintended organization of ignorance’, *Technology in Society* (2007) 2(29), pp. 181–8; Emmanuel Henry, Valentin Thomas, Sara Angeli Aguiton, Marc-Olivier Déplaude and Nathalie Jas, ‘Beyond the production of ignorance: the pervasiveness of industry’s influence in the shaping of chemical regulatory policies’, *Science, Technology, & Human Values* (2021) 5(46), pp. 911–24.

⁸ John Abraham and Rachel Ballinger, ‘The neoliberal regulatory state, industry interests, and the ideological penetration of scientific knowledge: deconstructing the redefinition of carcinogens in pharmaceuticals’, *Science, Technology, & Human Values* (2012) 5(37), pp. 443–77; Jean-Noël Jouzel and François Dedieu, ‘Rendre visible et laisser dans l’ombre’, *Revue française de science politique* (2013) 1(63), pp. 29–49; Nathalie Jas, ‘Une histoire d’accommodements: La constitution d’une expertise internationale sur les additifs et contaminants alimentaires dans les années 1950’, in Soraya Boudia and Emmanuel Henry (eds.), *La mondialisation des risques*, Rennes: Presses universitaires de Rennes, 2015, pp. 45–60; Annie Thébaud-Mony, ‘Histoires professionnelles et cancer’, *Actes de la recherche en sciences sociales* (2006) 3(163), pp. 18–31.

⁹ Frederick R. Davis, *Banned: A History of Pesticides and the Science of Toxicology*, New Haven, CT: Yale University Press, 2014; Christopher Sellers, *Hazards of the Job: From Industrial Disease to Environmental Health Science*, Chapel Hill: University of North Carolina Press, 1997; Angela N.H. Creager, presentation of the upcoming book *Environment, Mutation, Cancer: A History of the Ames Test*, workshop seminar of Cermes3, 14 March 2025, Villejuif, France; Annamaria Carusi, ‘Chemicals regulation and non-animal methods: displacing the gold standard’, *Wellcome Open Research* (2024) 9, p. 167; Shostak, op. cit. (5).

international programmes for the assessment of chemicals proliferate from the 1960s onward.¹⁰ Extending these findings, I argue that these organizations proliferate while connected to each other as experts, cases, concepts and data have been in constant circulation between them. Part of the transnational network of institutions that emerged over the 1970s and 1980s for assessing the carcinogenicity of chemicals will serve as a case study here. During this period, and while watching each other, the National Toxicology Programme in North Carolina, the IARC in Lyon, the Occupational Safety and Health Agency (OSHA) and later the United States Environmental Protection Agency (EPA) in Washington stated that a two-year study on animals can constitute proof of carcinogenicity. In doing so, they set up an institutional order with a division of labour relying on a specific definition of carcinogenicity.

I draw on several thousand documents that connect these institutions, which have been collected within the IARC archives in Lyon. Created in 1965, IARC has progressively positioned itself on an international scale as an intermediary between scientific laboratories and regulatory agencies, in Europe and the United States. It is the origin of the IARC Monographs series, which are critical syntheses of the available scientific literature on the carcinogenicity of several types of exposure. Since its inception, the IARC Monographs Service has sought to establish criteria for defining legitimate evidence of carcinogenicity. The ‘preamble’ introducing each monograph, which establishes hierarchies between studies and knowledge of different types, has been and remains at the heart of intense tensions and negotiations.

Here, I analyse the institutional dynamics by which animal studies were set up as legitimate evidence of carcinogenicity, alongside the evidence from epidemiological studies conducted on humans. Central to this evolution was the work of Lorenzo Tomatis, the creator of the monograph programme whose early years at IARC I recount. Benefiting from a peak in the production of these studies, a transnational network of experts sought to establish their value through the intense work of methodological standardization and institutional linkages. This standardization effort contributed to the adoption of the same criteria by several organizations that formed a network of cross-legitimization. Finally, this stabilization of the regulatory order was quickly put under pressure by the rise of new data whose advocates questioned the legitimacy of animal studies.

Animal studies at the heart of carcinogen classification

Lorenzo Tomatis was born in 1929 in Sassoferrato, in northern Italy. He began his medical studies at the University of Turin in the late 1940s, later specializing in preventive and occupational medicine. In the late 1950s, he relocated to the United States to train in animal toxicology at a prestigious laboratory in Chicago. Unable to secure a research position in Italy upon his return, he applied to the IARC and was hired in 1967.

Founded two years earlier, the IARC was governed by a council comprising representatives from each funding nation (originally France, Great Britain, the United States, Italy and the Federal Republic of Germany) and the WHO’s director general. This council elects a new director general every five years. The institution’s routine activities, designed and proposed by a scientific council, are divided into specialized units, such as immunology, epidemiology and biological carcinogens. Tomatis led the ‘chemical carcinogenesis’ unit, which was responsible for testing the carcinogenicity of synthetic substances on animals.

¹⁰ Nathalie Jas, ‘Gouverner les substances chimiques dangereuses dans les espaces internationaux’, in Dominique Pestre (ed.), *Le gouvernement des technosciences: Gouverner le progrès depuis 1945*, Paris: La Découverte, 2014, pp. 31–63.

At its inception, the monographs project was a minor initiative, funded mainly by the National Cancer Institute in the United States. Tomatis, leveraging his connections there, convinced them to support his project. The goal was to create for the WHO a list of carcinogenic substances based on available international literature. This list explicitly aimed to meet an urgent need for researchers, industrial hygienists, pharmaceutical companies, and health ministries globally. Initially, Tomatis's ambition was to simply establish this list, even if the first step was somewhat mundane.

Monographs were and still are overviews of the available scientific literature. Each IARC monograph was dedicated to a potentially carcinogenic exposure and was prepared and published with one or more other monographs in volume form. Since the first volumes, the writing of these expert reports has followed much the same procedure. The permanent members of the Monographs Service would first draw up a list of exposures to be appraised, then assign some twenty external scientists the task of writing preparatory summary papers on specific points in the literature. After this initial work phase, this group of experts would meet for a week at IARC headquarters in Lyon to discuss these preparatory documents and draft the volume of monographs envisaged. As IARC is a scientific research organization, these reports have no official regulatory value; that is, they do not automatically bind public policies on the control of carcinogenic exposures. Nevertheless, the monographs are tools for health agencies and public authorities, and are also used by economic players, trade unions, courts and activist groups.

When Tomatis created the monographs series, the overarching goal was to create an encyclopedia of carcinogens, focusing on quantity. A notable feature of the monographs was their heavy reliance on animal studies. By 1973, of about eighty agents evaluated in the first five volumes, only 35 per cent had human epidemiological studies, while almost 100 per cent had animal studies. This focus stemmed from several factors. The project's initiators, including Lorenzo Tomatis, were primarily toxicologists with expertise in rodent laboratory studies. Additionally, practical constraints influenced this direction: human epidemiological studies on industrial exposures were rare, lengthy, difficult to conduct (often obstructed by factory management), less capable of isolating single-substance exposures, and more expensive. Moreover, epidemiological studies often focused on lifestyle factors and personal habits, such as smoking or food consumption, rather than the exposures to industrial chemicals on which most of the monographs were focused. If animal studies could not be extrapolated to humans, then the monographs were in danger of losing their value.¹¹ It is not surprising that, during that period, the statement mentioned in the epigraph regarding the value of animal evidence was incorporated into the scientific guidelines of the monographs. These studies became central to the IARC's carcinogen evaluations. During the 1970s, the secretariat built a classification scheme for carcinogens to standardize its evaluations. It initially differentiated 'sufficient' and 'limited' evidence in lab animals, then extended this framework to human evidence. Simultaneously, expert groups invited by the monograph programme's secretariat developed a system merging evidence from human and animal studies, creating categories: (1) 'carcinogenic', (2A) 'probably carcinogenic', (2B) substances with 'suggestive evidence' of carcinogenicity and (3) 'unclassifiable' as to their carcinogenicity. This taxonomy developed through collaboration with regulatory bodies and the monographs programme's approach became *de facto*, though indirectly, a regulatory tool, even if IARC itself did not have any regulatory prerogatives. For instance, the Occupational Safety and Health Agency (OSHA) in the US adopted a similar system. OSHA often aligned its agenda with the monograph programme's, and IARC classifications thus often mirrored OSHA's, prompting US regulatory actions and enhancing the influence of this collaborative system.

¹¹ Valentin Thomas, *Classé cancérigène*, op. cit. (1), pp. 86–97

The emergence of a network of institutional interdependence

Gradually, a transnational institutional complex was emerging in which evaluation files on potential carcinogens were constructed and circulated, with animal studies serving as the primary fuel. The National Cancer Institute (NCI), the most important cancer research centre in the United States, was part of this complex. The NCI had agreed to be the main funder of the monograph programme. In addition, one of its research activities was based on its animal experimentation programme. At the end of the 1970s, this experimental programme became autonomous, and was entrusted to a new institution, the National Toxicology Program (NTP).

Tomatis was informed of the project from the outset, and welcomed it, since the creation of an institution with such a mission guaranteed a steady supply of animal studies. The NTP was also linked to the monograph programme by joint experts. After leaving his post at the monographs secretariat, James Huff, an American toxicologist and Tomatis's right-hand man in the late 1970s, was recruited to the NTP to conduct animal experiments. He was one of the architects of the direct link between the production of animal studies at the NTP and their use in the IARC Monographs. In 1982, he wrote to Tomatis:

Because I (and the NTP) remain strongly interested in the Monographs program and associated activities (and since much of the research/testing that we do reaches eventually your Agency), may I request that we be kept informed about upcoming meetings (or those planned) and especially what chemicals are being considered as candidates. We may be able to alert you regarding ongoing or planned studies.¹²

As Huff explicitly stated in this letter, not only did the animal studies carried out at the NTP feed into the monographs programme, but also it would be a good idea, he explained, to plan this relationship, ensuring that the NTP could be made aware of the monographs under consideration, so that it could adjust its testing programme accordingly. At the time of writing, the NTP testing programme had already produced over two hundred long-term studies on rats and mice, and the IARC Monographs secretariat had every interest in maintaining a good relationship with this institution. What was at stake here was the creation of a transatlantic chain of legitimization via interdependent validation, assessment and data-producing processes: IARC had helped to develop and establish experimental standards, which the NCI and NTP consecrated and legitimized through their studies, themselves consecrated by IARC in its monographs, on whose agenda the NTP adjusted itself.

These interdependent links only grew stronger as the monographs became part of the US regulatory landscape. Thus, after becoming institutionalized in the workings of OSHA and the NTP, the programme's classifications were also integrated into the workings of the EPA. Founded in 1970, the Environmental Protection Agency began corresponding with the monographs programme in 1977. Indeed, on his arrival in Lyon, Huff requested that the documents he was accustomed to receiving from the EPA be transferred to his new address.¹³ He used the opportunity to describe the activities of the monographs to his contact at the US environmental agency, 'in case [he] wasn't familiar with them'. It was a special time for the EPA, which was in the midst of implementing its Toxic Substance Control Act (TSCA). The TSCA was an imposing regulatory scheme, designed to enable the agency to control the toxicity of all chemical substances in circulation or entering the US market. As early as May 1976, the EPA adopted a definition of carcinogenic substances, but the way in which the system was to operate was still relatively vague.¹⁴ Although the initial proponents of

¹² IARC, C2/12, Jacket 47–8, letter from J. Huff to L. Tomatis, 23 February 1982.

¹³ IARC, C2/12, Jacket 28a–31, letter from J. Huff to US EPA, Office of Pesticide Program, 3 June 1977.

¹⁴ *Federal Register* (25 May 1976) 41(102), pp. 21402–5.

this project to control the chemical-substances market were forced – by various pressures, difficult negotiations and an even more difficult start – to lower their ambitions, this piece of legislation was nonetheless implemented.¹⁵

In particular, the EPA could request toxicity testing of certain substances for which it believed there was a carcinogenic risk. It was into this breach that Huff tried to insert himself, informing the agency that of the fifteen chemicals for which in-depth examinations had been requested, eight had already been evaluated in the monographs, which he enclosed with his letter, and five others would be evaluated in the coming months.¹⁶ This solicitation strategy had an effect. Three months later, the head of the EPA's Bureau of Chemical Substances met Tomatis in person in Lyon.

EPA bureaucrats considered whether or not to adopt the IARC classification criteria, which they did with adjustments to soften it in the second half of the 1980s.¹⁷ IARC's 'possible', 'probable' and confirmed carcinogens could then more easily be incorporated into the North American lists of substances to be controlled. Having developed its classification system in close collaboration with OSHA and fed it into the NTP, IARC then exported it to the EPA. As a result of this institutional interdependence, a substance identified as carcinogenic in rodents by an NTP study was likely to end up on both international and US regulatory lists of carcinogens.

For instance, in 1987, drawing on animal NTP studies, the IARC classified di(2-ethylhexyl) phthalate (DEHP) – one of the most commercially successful phthalates, with 130,000 tons produced in the United States in 1986 – as 'possibly carcinogenic'. This prompted the EPA to adopt a similar classification and establish acceptable daily intakes (ADIs) for DEHP in food products and set threshold levels for drinking water.¹⁸ These measures applied to areas where DEHP had previously faced very few restrictions.¹⁹

Competition from mechanistic studies

The first volumes of the monographs included a section generally entitled 'Other relevant biological data', which did not contain the main results of animal or epidemiological studies. From Volumes 1 to 7, this section was dedicated to information on the agent's metabolic trajectory. In other words, how did the body, whether human or animal, process the agent? Was it transformed into something else, did it remain in the body? How was it eliminated? And so on. The integration of this information made it possible to take into account the fact that many carcinogens, as the literature showed, are only activated in the presence of a metabolic action by the exposed body.²⁰ Later, in Volume 8 in 1974, the section included for the first time data on the agent's 'mutagenic' character; that is, its ability to alter DNA.²¹ This kind of data, because it provided an understanding of the mechanisms of carcinogenesis at the cellular level, was referred to by the scientific community as 'mechanistic data'. At first, these data occupied a secondary place in the scientific evaluation criteria of the programme. Epidemiological and animal studies continued to prevail, and these alone could justify putting agents on the agenda. Indeed, the reliability and even significance of the tests

¹⁵ Angela N.H. Creager, 'To test or not to test: tools, rules, and corporate data in US chemicals regulation', *Science, Technology, & Human Values* (2021) 5(46), pp. 975–97.

¹⁶ IARC, C2/12, Jacket 28a–31, letter from J. Huff to D. M. Costle, 25 July 1977.

¹⁷ US EPA, *Guidelines for Carcinogenic Risk Assessment*, 1986, pp. 17–18; see also Demortain, *The Science of Bureaucracy*, op. cit. (3), pp. 203–7.

¹⁸ US EPA, 'Health effects assessment for selected phthalic acid ester', *Technical report Data* (1987), pp. 28–9.

¹⁹ US EPA, 'Ambient water quality criteria for phthalates esters', *EPA Report* (1980), p. c-53.

²⁰ This followed a then twenty-year research effort made in the scientific field. For an early example see James A. Miller and Elizabeth C. Miller, 'The carcinogenic aminoazo dyes', *Advances in Cancer Research* (1953) 1, pp. 339–96.

²¹ IARC *Monographs* (1973) 8, pp. 19–20.

that produced mechanistic data, most of which were very inexpensive in terms of time – hence their generic name of short-term tests, as opposed to long-term animal experiments – remained extremely uncertain.

IARC scientists from the monograph programme therefore wondered what place this mechanistic knowledge should be given in the classification system that was being developed. Especially as these short-term tests were gaining increasing acceptance within scientific and regulatory institutions worldwide, whether in industrial, academic or regulatory fields. The Ames test, for example, named after the scientist who developed it in 1973 at the University of Berkeley, became a reference in just a few years.²² Extremely rapid and considerably less costly than long-term animal or epidemiological studies, the Ames test made it possible to detect the mutagenic nature of synthetic or non-synthetic chemical compounds by a very simple laboratory procedure. Moreover, the test stains were made freely available by its author. From the late 1970s onwards, manufacturers and health agencies began to use this test (also known as the Salmonella test) as a basis for their substance pre-selection policy, to determine whether or not to take their evaluation further, or to put an end to research and development processes.²³ At the NTP, for example, which was just starting up its animal experimentation programme, the Ames test was one of the preferred methods for determining which compounds would or would not be subject to long-term animal experimentation.²⁴

At the time, however, there was no consensus on the value of mechanistic data, and it was only gradually that the IARC programme established its position on the matter. In fact, it became more and more difficult not to take a position on the use of these tests, as the issue took on such importance within its network. Several of the monographs' most regular contributors, for example, were very insistent on the need for the secretariat to tackle the issue of mechanistic knowledge head-on.²⁵ At the NTP, the idea of including these data was also gaining ground, and was linked to a critique of animal studies:

As you realize, I firmly believe that animal testing alone is no longer a sufficient basis on which to formulate an evaluation of the potential hazard of a chemical. In this regard you may be interested to learn that in the last series of bioassays that we evaluated, vinylidene chloride was found to be noncarcinogenic in rats and mice and C.I. solvent yellow 14 was found to be noncarcinogenic in mice. Both of these have been repeatedly positive in other tests. Thus, I would offer you every encouragement and whatever assistance I can provide in developing more comprehensive approaches, particularly incorporating other relevant biological data, to the evaluation of carcinogenic risk of chemicals.²⁶

The secretariat convened groups of experts to consider the issue. They came up with three recommendations. First, data from short-term tests should henceforth be associated with a scale of levels of evidence similar to that for animal and epidemiological data: 'sufficient', 'limited' and 'inadequate'. Second, mechanistic data alone could not justify putting one exposure on the agenda and could only be used as a complement to animal and human

²² Angela N.H. Creager, 'The political life of mutagens: a history of the Ames test', in Soraya Boudia and Nathalie Jas (eds.), *Powerless Science? Science and Politics in a Toxic World*, New York: Berghahn Books, 2014, pp. 46–64; Creager, this issue.

²³ For an insight into the shift provoked by this test and its successors in the regulatory process see Larry D. Claxton, Gisela de A. Umbuzeiro and David M. De Marini, 'The Salmonella mutagenicity assay: the stethoscope of genetic toxicology for the 21st century', *Environmental Health Perspectives* (2010) 11(118), pp. 1515–22.

²⁴ IARC, C2/12, Jacket 42–4, letter from L. Tomatis to R. Dall, 3 March 1979.

²⁵ IARC, C2/12, Jacket 49–52, letter from P.N. Magee to L. Tomatis, 23 January 1982.

²⁶ IARC, C2/12, Jacket 45–6, letter from G.M. Williams to L. Tomatis, 20 February 1981.

studies. Third, it was agreed that, ‘In some cases, the working group considered that the known chemical properties of a compound and the results from short-term tests allowed its transfer from Group 3 to 2B or from 2B to 2A’.²⁷

In practical terms, this meant that an agent for which animal and human data would normally have been classified as ‘unclassifiable as to carcinogenicity’ or as ‘possibly carcinogenic’ could now, thanks to mechanistic data, be upgraded to ‘possibly’ or ‘probably’ carcinogenic. It was not possible to make the reverse move, to downgrade an agent on the basis of mechanistic data. But this strategy did not last long. In 1991, another committee of experts made a major change to the way in which these mechanistic data can be used to modify classifications. It was still possible, using these data, to upgrade an agent from category 3 to 2B, 2B to 2A and, newly, 2A to 1. However, what had previously been impossible became permissible under the new doctrine, to downgrade an agent from category 2B to category 3. Given the links between IARC’s classification system and those of regulatory agencies, particularly in the US, such downgrading was tantamount to preventing a chemical from showing up on the radars of regulatory institutions using IARC’s classifications.

The new monograph guidelines provided for such downgrading in one particular case only. It was possible to downgrade an agent if the evidence was inadequate in humans and sufficient in animals, but there was nevertheless ‘strong’ evidence that the mechanisms of carcinogenicity that operated in laboratory animals did not operate in humans.²⁸ In other words, animal evidence, which was so central to the construction of the programme’s scientific, political and institutional project, and on which the value of the monographs was largely based, was in danger of being devalued. Yet Tomatis, who was the prime mover behind this hierarchy of evidence, was at the time director general of IARC, and it is therefore surprising that this discrete but significant about-turn should have taken place during his tenure.

Questioning animal studies

To grasp this change in the programme’s scientific doctrine, one needs to understand the disruptions that took place within the scientific and regulatory space in which it operated. Between 1982 and 1991, very soon after its creation, the NTP, which was the main provider of animal data for the monograph programme and the main institution legitimizing these studies, was destabilized. This opened the door to the use of mechanistic data at the expense of the value of animal studies, which came under attack from a number of actors.

First, the NTP’s productivity, dazzling during its first year of operation, collapsed in a very short time.²⁹ In 1978 and 1979, about a hundred long-term studies were published or were in progress at the NCI and/or the NTP, as the testing programme was transferred from one institution to another during this period. The number then oscillated between two and thirty during the 1980s, rarely exceeding twenty studies in the 1990s and ten in the 2000s. The abundant source of new animal studies – ones that were in the public domain – had thus rapidly dried up.

This trend was also true on a global scale. The monographs secretariat could see this through its monitoring of the animal studies being carried out in the 120 or so public laboratories with which it is in contact. Over 170 chemicals were being tested in 1973, over 820

²⁷ IARC Monographs (1982) Suppl. 4, p. 14.

²⁸ IARC Monographs (1992) 55, p. 35.

²⁹ I have compiled these figures from the list of studies available on the institution’s website, at <https://ntp.niehs.nih.gov/publications/reports/index.html?type=Technical+Report> (accessed 30 June 2024).

in 1976, and 1,100 in 1979. However, this productivity declined throughout the 1980s and 1990s, barely reaching five hundred compounds under test in 1996.³⁰

In addition to this brutal decline, due in part to financial issues, the quality of the NTP's work was also called into question. One of the most violent episodes occurred in 1982. The NTP had just completed a long-term study on methylene chloride, an agent used both in aerosol manufacture and in the production processes of decaffeinated coffee. The gavage study showed a significant increase in pancreatic cancer in two species. Such a verdict, reported the *New York Times*, could lead the US Food and Drug Administration (FDA) to ban the use of this product.³¹

In its report, the panel of evaluators of the NTP study, made up of internal and external participants as required by procedure, made a number of remarks on methodological points, and in particular on the possible carcinogenic role of corn oil, with which the substance was administered to the rodents and which could have biased the results of the experiment. The National Food Association, an industry association that had attended the panel, seized upon this flaw and attempted to torpedo the study, which helped to prevent publication of the report.³² The affair took on major proportions, and the NTP came in for fierce criticism of the quality and general usefulness of its scientific work.

These attacks came from several segments of the (agro-)food industry, who took advantage of the methylene chloride episode to attack more broadly the legitimacy of an institution, the NTP, whose studies had on several occasions justified bans or restrictions on their products.³³ They also came from research institutions such as MIT and the Food Research Institute at the University of Wisconsin–Madison. A researcher from the University of Massachusetts wrote to the FDA and the NTP,

The apparent reliance on long term animal feeding studies has been justified in the past as being the 'only game in town'. We have accepted this in spite of the uncertainty of extrapolation from high to low doses combined with the uncertainty of a second extrapolation from animal to humans ... The NTP is a very expensive and very visible program. Regardless of the caveats, it is regarded in the public eye as the ultimate. Yet, I fear the wheels have been set in motion to destroy its credibility in the eyes of the scientific community. We cannot afford a scientific bust of this magnitude. The stakes are too high!³⁴

The effect, and sometimes the main intention, of these attacks was to isolate the NTP by detaching it from the regulatory circuit that also made the FDA dependent on its studies. These letters can be found in the archives of the monographs programme, as Tomatis received them from an FDA official who urged him to consider carefully the reliability of the NTP in the following years:

My personal belief is that if another 'methylene chloride type' bioassay is revealed in terms of short-comings and the material is of paramount importance to an industry,

³⁰ Compilation of the series 'Information bulletins on the survey of chemicals being tested for carcinogenicity', nos. 1–4, 5–17.

³¹ Marian Burros, 'Food notes', *New York Times*, 30 June 1982, p. 11.

³² NTP Board of Scientific Counselors, 'Summary minutes from peer reviews of draft technical reports of long-term carcinogenesis bioassays by the Technical Reports Review Subcommittee and Panel of Experts', 22 September 1982, at https://ntp.niehs.nih.gov/ntp/about_ntp/bsc/trrs/1982/sept/82sept22trrsmin_508.pdf (accessed 5 September 2020).

³³ Sarah A. Vogel, *Is It Safe? BPA and the Struggle to Define the Safety of Chemicals*, Berkeley: University of California Press, 2013.

³⁴ IARC, C2/12, Jacket 53–4, letter from F.J. Francis to A.H. Hays and R. Dall, 5 January 1982.

then there would be enormous pressure for Congress (at least a subcommittee) to intervene with hearings concerning the validity of the NTP bioassays, etc. With this current administration and their well known feelings concerning industry, the net effect, I believe, would be to institute a type of 'freeze' whereby nothing will transpire regarding NTP-bioassays till questions of '*validating the NTP bioassay*' take place, etc. This aspect alone will consume a treasure and at least 4–5 years. I'll talk more about this when I see you but suffice it to say that the matter is serious.³⁵

In short, through concerns in the US (especially about the market for decaf coffee), the validity of the animal carcinogenicity assay had been put into doubt, which in turn raised questions about the IARC's authority in determining whether substances could cause cancer. These stakes make clear why the monographs secretariat could not accept a use of mechanistic data that would merely confirm animal studies, especially given that it was able to triangulate with epidemiological data in only a very few cases. In fact, the opening up in 1991 of the possibility of downgrading substances on the basis of mechanistic knowledge reinforced the questioning of animal studies.

In 1996, IARC's new director general, who had been recruited on a scientific line that broke with Tomatis's, appointed a new head of the monographs programme, Jerry Rice. Rice was a toxicologist, having spent most of his career at the NCI. But unlike Tomatis, he had built this career on the idea that certain cancer mechanisms were specific to rodents and that, consequently, studies revealing carcinogenic effects in animals were not necessarily extrapolatable to humans. One of the first steps Rice took on his arrival at the monograph programme was to convene a committee of experts to modify the classification criteria along these lines, based on certain controversial mechanistic theories.³⁶ The committee's report clearly stated that 'the possibility that an agent causes cancer in animals through a mechanism that does not operate in humans must be taken into account'.³⁷ The consequences were immediate. In the late 1990s and the early 2000s, a handful of compounds for which animal studies could have supported a classification as 'possibly carcinogenic' were instead judged 'unclassifiable as to carcinogenicity'. DEHP, mentioned above, was one of these substances.

These moves and revisions to scientific guidelines sparked significant struggle and resistance. In the early 2000s, critics of these policy changes published a series of open letters in the *International Journal of Occupational and Environmental Health* and *Environmental Health Perspectives*. Among the signatories were users of the monographs, including environmental NGOs and scientists active in occupational-health advocacy networks, who relied on the monographs to support their campaigns. Tensions declined after Rice had left his post as head of the monograph programme. The value of animal studies at IARC depended on the power relations within and among institutions as well as scientific disputes. Indeed, in 2011, DEHP was once again classified as a 'possible carcinogen' by a panel of experts who set aside the justifications of their predecessors who had based their declassification on mechanistic studies.

Conclusion

As the case of identifying and regulating carcinogenic substances shows, scientific studies have no value in themselves. Animal studies became central in this field for reasons that

³⁵ IARC, C2/12, Jacket 53–4, letter from L. Fishbein to L. Tomatis, 9 September 1983, emphases added.

³⁶ Valentin Thomas, 'Defects in doubt manufacturing: the trajectory of a pro-industrial argument in the struggle for the definition of carcinogenic substances', *Science, Technology, & Human Values* (2021) 5(46), pp. 998–1020.

³⁷ IARC, *Scientific Publications*, 1997, n. 147.

went far beyond their scientific content. They were produced in greater numbers than epidemiological studies, and less expensively, and flooded the scientific market in just a few years. Several institutions made these studies the core of their classification systems, creating equivalences between those systems. This further reinforced the centrality of animal studies, which became the keystone of an institutional architecture for the control of carcinogenic substances on a transnational scale. But what was done could also be undone. The value of animal studies was challenged almost as soon as it was stabilized, by the convergence of several factors: first, the ever-increasing production of mechanistic studies, and the promise they brought of rapid, inexpensive identification of the causes of cancer; second, the drastic reduction in the production of public animal studies from the 1980s onwards, in the most important institutions in charge of such production; and finally, a direct challenge to the scientific validity of animal studies, in terms of both their protocol and their ability to mean anything to humans. This sequence involved much more than scientific competition between different types of data. Challenging animal studies has had the effect of calling into question the institutional relationships that put these studies at the heart of debates, and guaranteed their value. Despite these disruptions, animal studies have remained central elements of the regulatory arena, and mechanistic studies have gained a place alongside them, without replacing them. The demonstration in this article sheds light on the issue but does not exhaust it. There is something largely absent from the archives, something neither scientists nor regulatory officials mention in the traces they left for historians. Replacing mice with laboratory cells also means neutralizing a tangible image of cancer development – an image that was central in attaching carcinogens, both visually and affectively, to tumours.

One could hypothesize that this shift generated two opposing movements. On the one hand, a resistance to the emergence of a more technical imaginary – one shaped by medical imaging and less capable of mobilizing support around the cause of carcinogens. On the other hand, an acceleration of criticism against animal testing in the name of combating animal suffering, an idea later echoed in numerous calls for a ‘toxicology for the twenty-first century’.

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