(2), p. 501, note e; (14); and notes 7 and 8 of my letter. Further, with the apparent exception of electric distribution costs (21), the newer studies Gallagher cites update only escalation and indirect costs; the 1975 base costs and schedules will not be updated until the spring of 1979.

17. I assume a 1.1-gigawatt dual unit with a cooling tower, built outside the Northeast, as the architect-engineer's 25th unit and the country's 124th commercial construction-permit issuance (134, including 16 under turnkey contracts, had been issued by 31 August 1976). The *empirical* cost [smoothed as in (15)] of plant 58, commissioned in December 1977, was $920/kWe in 1976 steam-plant dollars, confirming the conservatism of my $929 for 1976 *ordering* and zero real escalation.
18. See, for example, note 8 of my letter and, in terms of total cost per kilowatt-hour sent out, C. L. Rudasill, "Coal and nuclear generating costs." [Report No. PS-455-SR, Electric Power Research Institute (EPRI), Palo Alto, Calif., April 1977)].
19. EPRI's average coal cost (18), derived from a special Bechtel study, is $595 to $721 per kilowatt electric, comparing well with my $607. Komanoff has shown [(15), "Responses to PSE & G Requests 31 & 35," 27 December 1978] that the average U.S. historical ratio of nuclear-to-coal capital costs per kilowatt electric installed is 1.51 (1.72 without an industry-derived 16 percent addition for coal plants without scrubbers). My own nuclear-to-coal ratio, 1.53, is consistent with this historical 1.51 and exceeds the ESPM's unrealistically low 1.23 because of 2 years' differential escalation at 13 percent per year in the Bupp & Treitel conversion from 1974 to 1976 dollars (1, 2). If we assume zero differential escalation after 1976, the EPRI-Bechtel 1977 coal cost of $595 to $721/kWe and the historical nuclear-to-coal ratio of 1.51 together imply a nuclear cost of $898 to $1089/kWe, averaging 7 percent above my $929/kWe. Thus in order to achieve a nuclear cost of only $929/kWe, coal would have to escalate *faster* than nuclear from 1977 to 1985 in order to reduce their ratio below historical levels. This implausible requirement indirectly confirms the conservatism of my reactor cost figure.
20. J. M. Gallagher, R. Barany, P. F. Paskert, R. G. J. Zimmerman, "Resource requirements, impacts, and potential constraints associated with various energy futures" (annual report to the Department of Energy, Bechtel National, Inc., San Francisco, August 1978; available from the National Technical Information Service, Springfield, Va.). The nuclear cost given, using the 7 percent and 9 percent annual escalation and interest rates that the authors assume, is $1110/kWe installed in March 1977 dollars. The ratio of this cost to their average coal cost (weighting high- and low-Btu-coal plants according to the ESPM's table 7-7) is 1.51, precisely the historical average and consistent with my argument (19).
21. This assumes costs (including escalation and interest) as given in (20) for all facilities; Bechtel's 0.65 capacity factor (13); the ESPM's 16.4 percent T & D losses (1); my fuel-cycle parameters (1) and initial core costs (1) ($100/kWe installed, inflated 7 percent to 1977 dollars); and the T & D modal splits (1) supplied by Gallagher on 4 October 1976. Per kilowatt electric of installed generating capacity, (20) then yields 1977 dollar costs for the reactor, marginal fuel-cycle facilities, transmission, and distribution of, respectively, $1110 (12 percent up from my value), $79 (3 percent down), $97 (5 percent up), and $290 (48 percent down). The updated costs thus agree quite well with those I obtained by escalating the ESPM's costs from 1974 to 1976 dollars with appropriate indices (1, 2)—except for distribution, whose base cost the update has inexplicably halved (16, 20) from a value Bechtel described in May 1976 as "based on quite detailed information, with both quantities and prices listed, [so] we are confident based on a thorough review . . . that the estimate is reasonable, given the assumptions used." ["Review of electric distribution costs" (memorandum to Brookhaven National Laboratory, Bechtel Corp.)]. Because the other capital costs agree so well, combining Gallagher's latest costs (20) with *my* 0.55 capacity factor and 10.7 percent T & D losses changes the whole-system nuclear cost from $2905/kWe delivered to $3204, only 8 percent below my $3495 (all in 1976 dollars, deflating the Bechtel values 7 percent); this difference arises from the changed distribution base cost. Thus *neither* substituting Bechtel's latest costs *nor* their ancillary assumptions for mine significantly changes my results, as Gallagher suggests.

Carcinogenicity of Phenacetin

The article (1) that Pedro Cuatrecasas quotes in his letter to *Science* (5 Jan., p. 6) is a summary of the activities carried out from 1971 to 1977 under the Programme on the Evaluation of the Carcinogenic Risk of Chemicals to Humans of the IARC (International Agency for Research on Cancer). The program is focused on the preparation of monographs in which all available experimental and epidemiological data, as well as data on use, production, and occurrence of individual chemicals are critically analyzed and summarized. The monographs end with an evaluation of the carcinogenicity of the chemical in animals and humans. Faced with a very large number of chemicals in our environment, we used certain criteria in our selection of those to be considered in the monograph program. It seemed reasonable to give precedence to chemicals for which (i) there is evidence of human exposure and (ii) there is some evidence of carcinogenicity in experimental animals or some evidence or suspicion of human risk.

It is clearly stated in a note to the reader at the beginning of each of the IARC monographs that "inclusion of a chemical in the monographs does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that a chemical has not yet been evaluated in a monograph does not mean that it is not carcinogenic."

If the reader consults volume 13 (2) of the IARC monographs, which has the subtitle "Some miscellaneous pharmaceutical substances," a few misunderstandings could perhaps be avoided with regard to the evaluation of phenacetin as being associated with the occurrence of cancer in humans. At the time phenacetin was evaluated, that is, 18 to 25 October 1976, the results of only one experimental carcinogenicity study on phenacetin (3) were available. No evidence of treatment-related tumors was found in this study, in which phenacetin was mixed in the diet of Berlin-Druckrey rats at a dose of 40 milligrams per animal per day. The results of another study indicated *N*-hydroxyphenacetin, a putative metabolite of phenacetin, is carcinogenic in rats, producing hepatocellular carcinomas (4). The evaluation of the carcinogenicity of phenacetin in experimental animals states: "In one limited study in which phenacetin was administered orally to rats, no carcinogenic effects were observed. One putative metabolite of phenacetin, *N*-hydroxyphenacetin, is carcinogenic in rats after

its oral administration: it produced hepatocellular carcinomas" (*2*, p. 150).

We were not aware at that time that the Wellcome Research Laboratories had undertaken a carcinogenicity study on phenacetin in mice. It is not clear from Cuatrecasas' letter if this study was already completed in October 1976 and could have been reviewed by the working group evaluating phenacetin. However, it would have been difficult to know of such a study since the material was not published and could not be traced by a search of the scientific literature. In the preamble of the IARC monographs, it is also stated that "anyone who is aware of data that have been published or are in press which are relevant to the evaluations of the carcinogenic risk to humans of chemicals for which monographs have appeared is urged to make them available to the Unit of Chemical Carcinogenesis, International Agency for Research on Cancer, Lyon, France." Since the monograph on phenacetin was published in April 1977, one may wonder why it has taken so long to attract our attention to a possible omission. It is also hard to understand why drug companies, and chemical industries in general, are reluctant to publish their results on experimental studies related to such important and widely used chemicals as medical drugs and other industrial chemicals.

Cuatrecasas also mentions a summary of the National Cancer Institute report on the bioassay of a mixture of aspirin, phenacetin, and caffeine, published in the *Federal Register* on 11 August 1978. I wonder how we could have considered this study in October 1976 or quoted it in our *Cancer Research* article, which appeared in April 1978.

In our article in *Cancer Research* we mention (p. 881), however, that "recent unpublished results indicate that phenacetin is carcinogenic in rats." Since then, the results of a long-term carcinogenicity test on phenacetin in Sprague-Dawley rats have been presented at two different meetings (*5*, *6*); these indicate that an excess of urinary tract and nasal cavity tumors was observed in rats treated with phenacetin.

As for the human evidence on phenacetin, Cuatrecasas makes reference only to one epidemiological study. In the IARC monograph on phenacetin, eight published case reports and ten epidemiological studies were summarized, and the interested reader may refer to these summaries on pages 147 and 149 of that monograph. The evaluation of the human data made in (*2*) was that "available data indicate that heavy use of analgesic mixtures containing phenacetin is associated with papillary necrosis of the kidney and suggest a relationship between such use and the development of transitional-cell carcinoma of the renal pelvis." It was on the basis of this evaluation that phenacetin was included in table 2 of our article in *Cancer Research*, listing chemicals or industrial processes associated with cancer induction in humans.

If, as I have said above, drug companies and other chemical industries would publish the results of studies they have carried out on their products, such associations could be better established, and some misinterpretations might be avoided.

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References

1. L. Tomatis *et al.*, *Cancer Res.* **38**, 877 (1978).
2. *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man*, vol. 13, *Some Miscellaneous Pharmaceutical Substances* (International Agency for Research on Cancer, Lyon, France, 1977).
3. D. Schmähl and A. Reiter, *Arzneim. Forsch.* **4**, 404 (1954).
4. I. C. Calder, D. E. Goss, P. J. Williams, C. C. Funder, C. R. Green, K. N. Ham, J. D. Tange, *Pathology* **8**, 1 (1976).
5. H. Isaka, H. Yoshii, Y. Kaneko, M. Koike, A. Outsuiji, M. Koura, K. Sugiyashu, *Proc. Jap. Cancer Assoc. 37th Annu. Meet.* (No. 21) (1978).
6. H. Isaka, *Abstracts of the XII International Cancer Congress* (Buenos Aires, October 1978), vol. 1, No. 24, p. 40.

Cuatrecasas, a representative of the pharmaceutical company Burroughs Wellcome, in his letter of 5 January, does not cite some recent published results of clinical and epidemiological as well as experimental studies with phenacetin and phenacetin-containing analgesics. More than 100 cases of renal pelvic tumors in abusers of phenacetin-containing analgesics have been reported in the literature (*1*). Studies of the Swedish population strongly indicate a relationship between high intake of phenacetin-containing analgesics and the development of urothelial renal pelvic tumors (*2*, *3*). Also 42 primary tumors of the urinary bladder and four of the ureter have been reported in such patients (*4*). In an experimental study, four ear-duct tumors and five mammary adenocarcinomas were induced in Sprague-Dawley rats after long-term feeding with 0.535 percent phenacetin in the diet. One control rat developed a mammary adenocarcinoma (*5*). Tumors in these locations have been induced by aromatic amines chemically related to phenacetin, which is an aromatic amide (*6*). Isaka *et al.* (*7*) reported a 71 percent incidence of malignant tumors in Sprague-Dawley rats fed with 2.5 percent phenacetin in the diet, and 36 percent in the rats fed with 1.25 percent phenacetin in the diet. The authors concluded, "it is a fact beyond controversy that phenacetin is a carcinogenic chemical." We have recently completed a study (*8*) in which male Sprague-Dawley rats have been fed with 0.535 percent phenacetin in the diet for up to 117 weeks. We obtained a tumor incidence similar to what was reported by Isaka *et al.* (*7*).

One reason why relatively few tumors were found in the National Cancer Institute study may be that a mixture of aspirin, phenacetin, and caffeine was administered to Fischer rats, which are known to be less efficient in *N*-hydroxylation than Sprague-Dawley rats. This is considered to be the explanation of the lower susceptibility of Fischer rats to aromatic amine carcinogenesis (*9*). Phenacetin is an aromatic amide with *N*-hydroxylated metabolites. One of these, *N*-hydroxyphenacetin, has been shown to be a potent liver carcinogen (*10*). Nitrosation of phenacetin has been demonstrated and the nitroso compound has been shown to be tumorigenic (*11*).

Thus there are epidemiological studies in humans and metabolic and experimental data in rats that strongly support the assertion that phenacetin is a carcinogen. We therefore question the justification of keeping such a drug on the market.

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References

1. U. Bengtsson, S. Johansson, L. Angervall, *Kidney Int.* **13**, 107 (1978).
2. U. Bengtsson, L. Angervall, H. Ekman, L. Lehmann, *Scand. J. Urol. Nephrol.* **2**, 145 (1968).
3. L. Angervall, U. Bengtsson, C-G. Zetterlund, M. Zsigmond, *Br. J. Urol.* **41**, 401 (1969).
4. S. Johansson and L. Wahlqvist, *Acta Pathol. Microbiol. Scand. Sect. A* **85**, 768 (1977).
5. S. Johansson and L. Angervall, *ibid.* **84**, 375 (1976).
6. P. Shubik and J. L. Hartwell, *Survey of Compounds Which Have Been Tested for Carcinogenic Activity* (Government Printing Office, Washington, D.C., 1957).
7. H. Isaka, H. Yoshii, Y. Kaneko, M. Koike, A. Outsuiji, M. Koura, K. Sugiyashu, *Proc. Jap. Cancer Assoc. 37th Annu. Meet.* (No. 21) (1978).
8. S. Johansson and L. Angervall, in preparation.
9. C. M. King and W. T. Allaben, paper presented at the Symposium on Conjugation Reactions in Drug Biotransformation, Turku, Finland, July 1978.
10. I. C. Calder, D. E. Goss, P. J. Williams, C. C. Funder, C. R. Green, K. N. Ham, J. D. Tange, *Pathology* **8**, 1 (1976).
11. G. Eisenbrand and R. Preussmann, *Arzneim. Forsch.* **25** 1472 (1975).