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Joan Claybrook, President

November 1, 1996

Dockets Management Branch (HFA-305)
Food and Drug Administration
12420 Parklawn Drive Rm. 1-23
Rockville, MD 20857

RE: International Conference on Harmonization: Draft Guideline on Testing for Carcinogenicity of Pharmaceuticals; Docket No. 96D-0235

These comments are submitted by Public Citizen's Health Research Group and they include important input from Dr. William Lijinsky, a noted researcher in the field of carcinogenicity. His studies established important evidence of the carcinogenicity of nitrosamines which has led to a variety of regulatory actions including at the FDA, several involving pharmaceuticals.

Since the FDA "intends to adopt the ICH Steering Committee's guideline," it is critical to explain why, in its present form, it is unacceptably dangerous. Any decision to depart from the policy of using two rodent species in long-term experiments for determining carcinogenicity must be evidence-based. The proposal to change to using rat studies plus other ones which may–or may not–include a second species such as the mouse is contraindicated by current evidence.

The proposed guideline is also internally inconsistent because, despite the plan to stop routine mouse carcinogenicity testing, at Section 6 there is an admission that there have been instances in which mouse tumors were "the sole reason for regulatory action concerning a pharmaceutical" and that "data from this species may have contributed to a weight-of-evidence decision."

Need For Bioassays in Rats *and* Mice for Carcinogenicity Testing

Sources for information on substances carcinogenic in mice but not rats:
Huff J., CirVallo J., Haseman J., Bucher J. Chemicals associated with site-specific neoplasia in 1394 long-term carcinogenesis experiments in laboratory rodents. *Environ. Health Perspect.* 22, 247-270, 1991.

Ralph Nader, Founder
1600 20th Street NW• Washington, DC 20009-1001• (202) 588-1000

U.S.P.H.S. Seventh Annual Report on Carcinogens, 1994.

IARC Monographs, Supplement 7, Overall Evaluation of Carcinogenicity, Vols. 1 to 42, 1987.

The survey revealed that for 65 substances tested there was clear evidence of carcinogenicity in mice, but not comparable evidence in rats. Substances that were tested only in mice, but not in rats, were excluded. In 23 instances the pathological findings in rats were not entirely negative, but were dubious because of lack of statistical significance or because there was only an increase in "spontaneous" tumors, which have been shown to be highly variable in incidence and unreliable as a basis for determination of carcinogenicity (Lijinsky W., Riggs C.W., Walters P.T. *J. Toxicol. Environ. Health* 39, 527-538, 1993). In these cases, had only rats been the test species, the carcinogenicity of these substances would not have been revealed and accepted.

A chronic bioassay that results in a positive incidence of one or more types of tumor frequently gives insight into the susceptibility of certain organs (and cell types) to tumor induction. The addition of a second species (e.g. mice as well as rats) increases the probability that such organs will be identified. Although the well-known species variation in response to a particular carcinogen makes this effect less important in assessing human risk, there are many in the scientific and legal community who accept the results of animal studies and epidemiologic studies as congruent only when the target organ in animals and humans are the same.

Although money and effort would be saved by dispensing with the chronic bioassay in mice (or other species in addition to rats), it is certain that an equivalent amount or more will be spent on the many short term tests that are suggested as substitutes, without any probability that the latter will provide information as useful in assessing carcinogenic risk. For example, many carcinogens are also mutagens, because they are converted into powerful electrophiles. This does not mean that mutagenesis and carcinogenesis by these substances is the same process. Many carcinogens are not mutagens and some mutagens are not carcinogens.

There is no case in which the mechanism of induction of cancer by a carcinogen is known, although there are many hypotheses. A chronic bioassay in animals is useful in two ways: if negative, it offers considerable assurance that the carcinogenic risk to humans from exposure to the substance will be small (there is no absolute proof of safety); if positive, it permits some estimate of carcinogenic risk in human exposure, without knowledge of the mechanism by which the carcinogen acts. The metabolic parameters that can be measured easily might, or might not, have any bearing on the mechanism of tumor induction. The same is true of other biological, pathological or physiological effects that are claimed to be involved in cancer formation. Experiments in humans can only be undertaken with trepidation, so

circumspection is required in interpretation of studies that are "relevant to cancer in man."

Some carcinogens are extremely potent, so that only a few milligrams over the lifetime of a rodent can induce tumors in a significant proportion of treated animals. The nitrosamines in tobacco smoke are in this category, since less than 1 microgram per kilogram body weight per day in heavy smokers (much less than is required in rodents) is sufficient to induce cancer in a considerable proportion of them. In contrast, large doses of most carcinogens are needed to induce cancer in experimental animals, including non-mutagenic carcinogens. It would be surprising if the many types of carcinogens have more than a few characteristics in common although they might produce the same tumor end-point, often indistinguishable by pathologists. Those characteristics that confer carcinogenicity have yet to be revealed.

Although it is possible that in the future there will be evidence that other tests–in addition to the rat carcinogenicity studies–might be validated as more accurate predictors of carcinogenicity than the current combination of rat and mouse, at present there is no such evidence.

Since this possibility exists, such alternative tests should be explored *in addition to* the continued use of rat and mouse carcinogenicity studies. The idea of luring companies–who can well afford to do two-species carcinogenicity studies plus the newer not-yet-validated ones–by eliminating the requirement for mouse testing is a thinly-disguised but dangerous proposal. It comes from an advisory group, three of whose six members are the American, European and Japanese pharmaceutical industry trade associations and their influence is clear. It is unclear why the FDA and its European and Japanese counterparts have agreed to it.

Sincerely,

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