Nominations

NATIONAL TOXICOLOGY PROGRAM CHEMICAL TESTING

by

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These nominations repeat and extend previous UAW nominations for chronic bioassay testing.

The UAW believes that NTP should explore additional options for testing of chemicals beyond inclusion on this test list, and for funding this testing while using NTP protocols. In particularly, the UAW urges NTP to explore with EPA the use of authority under the Toxic Substances Control Act to promulgate test rules to compel producers of chemicals to provide funding for bioassays. In addition, NTP should explore alternatives to using public funds to test medicinal drugs and food additives which are sold for profit.

The UAW nominations are intended to assist in evaluating hazards and setting standards for inhalation exposure. A number of these nominations involve particulate material or mixtures. These are the most prominent exposures in the workplace. The UAW is aware that such studies are more demanding and expensive than typical oral bioassays. A testing scheme that uses uptake and distribution studies to compare inhalation and oral routes of exposure for chemicals where inhalation is vapor phase would be an acceptable alternative to inhalation bioassays. A testing scheme that uses short term studies to relate deposition by intratracheal instillation dosing to inhalation would be an acceptable alternative to inhalation bioassays for particulate.

The following nominations include agents previously not selected for testing. The UAW nominates these again. Also included are new nominations, including turpentine and MTBE. Some agents listed below appear on the chemical management reports in various stages of nomination and preliminary studies. It is not easy to determine which agents are really going to be bioassayed and which are not from this list.

1. **Trichloroethylene (in rats).** This material has been tested at least twice by gavage, and showed clear evidence for carcinogenicity in the mouse. The studies in rats were inadequate because increased mortality from kidney

toxicity occurring late in the studies prevented observation of carcinogenic effects. A good study in a second species is important for risk assessment purposes.

2. **Freon-113.** This material is also widely used as a cleaning solvent, especially in the electronics and defense industries. The existing bioassay is inadequate. Despite the claimed fluorocarbon phase out, this material is still being used. Many workers have substantial past exposures. A mortality study in a UAW-represented facility with large scale use of this material showed clear evidence for brain cancer associated with the jobs with highest freon-113 use. This material is listed as a pre-chronic study completed, awaiting further evaluation. However, no publication is listed.

3. **Turpentine.** Bioassay of turpentine, a natural product consistent of two terpenes is important because of widespread exposure and because of the potential to elucidate the alpha-2-microglobulin hypothesis. Turpentine is a member of the C10 hydrocarbon series.

   The alpha-2 hypothesis [incorrectly] discounts male rat kidney tumors because of lack of evidence of kidney toxicity in people exposed to alleged alpha-2 carcinogens such as gasoline. [This conclusion discounts the importance of mouse liver tumors observed in the gasoline bioassay as well.] However, the absence of direct evidence in people exposed to gasoline may arise from lack of studies in populations with appropriate exposure levels. However, the literature contains several reports of kidney toxicity in persons exposed to turpentine. Thus, the appearance or lack of appearance of kidney toxicity in rats with chronic exposure to turpentine vapors would complete a comparison.

4. **Methyl tert –Butyl Ether.** The Board of Scientific Counselors voted against listing this material because evidence for carcinogenicity was limited to male rat kidney tumors and mouse liver tumors. However, even though the mouse studies showed increased liver tumors, they were nevertheless inadequate studies because exposure was terminated after 18 months rather than two years. Therefore, evidence for tumors at other sites than the liver may have been lacking because of inadequate study. This nomination is for bioassay in both species in mice.

5. **Welding fume.** NIOSH has concluded there is epidemiological evidence of an association of welding fume exposure to lung cancer. Welding fume is a diverse collection of metal oxides and other particulate which is not metal. For risk assessment purposes, it would be important to test specific components. The specific agents to be tested are **iron oxide, copper oxide**, and **zinc oxide fume.**

6. **Cobalt dust.** Cobalt dust was extremely toxic in NTP pre-chronic studies. It appears in the management report, but it isn't clear whether this is on the way to be tested in the chronic bioassay. Cobalt exposure is responsible for hard metal disease in workers. Exposure occurs in tool grinding in the metal machining industry. This is a very high priority.

7. **Wood Dust** is acknowledged to be a human carcinogen. However, it is not regulated as such by any agency. In addition, wood dust causes non-malignant respiratory effects. There is a need to determine whether so-called "hard woods" (whatever the scientific classification would be) which are thought to be more dangerous than soft woods actually have different toxicity.

8. **Metalworking Fluid Constituents**

   There is sufficient evidence to conclude that machining fluids are carcinogenic in the occupational setting. The relative toxicity of constituents has not been determined. The following materials need to be tested by inhalation:

   Petroleum sulfonates (by inhalation)

   Non-ionic surfactants (by inhalation)

   Oil mist (by inhalation in conjunction with detergents)

   Triethanolamine (by inhalation). The available bioassay of triethanolamine was conducted by skin application. The dose which animals could tolerate was limited by skin irritation. The animals might have tolerated a substantially larger dose by inhalation, which is a primary route of exposure in the industrial environment. Therefore, the UAW requests an inhalation bioassay for triethanolamine.

9. **Sulfuric Acid Mist**. Sulfuric acid mist has been classified as known to be a human carcinogen in the occupational setting. This is probably the industrial chemical produced in largest quantity in the world. There is no animal test data which would permit evaluation of exposure response characteristics, or impact of mixed exposures.

10. **Mineral Particulate** The recent talc bioassay by NTP produced massive lung toxicity in both rats and mice at exposures close to the current OSHA permissible exposure limit, but did not achieve the maximum tolerated dose. As a result, evidence for carcinogenicity was found in only 1 of 4 experiments. Additional studies, perhaps with other mineral dusts should explore exposure response and synergism. Talc should be tested at a higher dose.

11. **Synthetic Mineral Fibers**

12. **Carbon fiber and Carbon Fiber Composite Particulate**

13. **Gasoline Exhaust Particulate** Diesel particulate is clearly carcinogenic in rats, and this result is supported by mutagenicity data and epidemiology. Parallel studies with gasoline engine exhaust particulate are lacking. These exposures may be important in the occupational setting.

14. **Synthetic Polymer Process Emissions** There are diverse combinations of exposures which need to be explored in the laboratory.

    formaldehyde plus particulate

    phenol formaldehyde resin dust (plywood, particle board)

    organic peroxides (for example MEK peroxide)

    polyester-polystyrene dust (in combination with fibrous glass)

    di-2-ethyl hexanol (plasticizer component)

15. **Di-glycidyl ether of bisphenol A.** The di-glycidyl ether of bisphenol A and various derivatives is a major component of epoxy resin adhesives and increasingly epoxy paints. Powdered epoxy paint has major potential for inhalation exposure. No bioassay has been performed. The di-glycidyl ether of resorcinol has been bioassayed by gavage and showed evidence for carcinogenic activity. Bisphenol A itself has been bioassayed, but this compound would not reflect the reactivity of its di-glycidyl ether. The primary human routes of exposure are skin contact and inhalation.

16. **Ethylene.** Ethylene is a substantial component of raw petroleum and natural gas. It is likely found frequently in the environment. Ethylene is, however, nominated exclusively for mechanistic purposes.

    It now appears that the complete series of chemicals with conjugated double bonds are highly carcinogenic: butadiene, isoprene, chloroprene, furan. For structure activity purposes, it would appear that any chemical containing this structure would be considered problematic. Halogenation is not necessary for carcinogenic activity.

    It would be important to complete the structure activity series for isolated double bonds as well. Vinyl chloride, vinylidene chloride, trichlorothylene, tetrachloroethylene, and tetrafluorethylene have all been tested and found to have some degree of carcinogenic activity. These compounds have substantially different chemical reactivity, but commentators have

concentrated on their organohalide bond as the moiety responsible for carcinogenic activity. It is plausible that the critical moiety is simple the isolated double bond.

Were ethylene to prove carcinogenic, then all chemicals with isolated double bonds, including vinyl acetate, cyclohexene, should be considered problematic.

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