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PEOPLE FOR THE ETHICAL TREATMENT OF ANIMALS

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Subject: Public Comments on the HPV Challenge Program Test Plan for 1,2-dimethyl-4-nitrobenzene (CAS No. 99-51 4) by BASF Corporation.

The following comments on the HPV Challenge Program test plan for 1,2-dimethyl-4-nitrobenzene (CAS No. 99-51 4) by BASF Corporation are submitted on behalf of People for the Ethical Treatment of Animals, the Physicians Committee for Responsible Medicine, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These health, animal and environmental protection organizations have a combined membership of more than ten million Americans.

1,2-Dimethyl-4-nitrobenzene (CAS No. 99-51-4) is an aromatic nitrogen compound that is used as an intermediate in the synthesis of pesticides. BASF Corporation proposes no additional testing for 1,2-dimethyl-4-nitrobenzene. Toxicity endpoints are characterized by existing data for 1,2-dimethyl-4-nitrobenzene and for its analogs, 2,4-dimethyl-1-nitrobenzene and the nitrotoluenes, 2-nitrotoluene, 3-nitrotoluene, and 4-nitrotoluene. 2,4-dimethyl-1-nitrobenzene is an isomer of 1,2-dimethyl-4-nitrobenzene, while the nitrotoluenes differ from the nitrobenzenes by having one rather than two methyl groups The physico-chemical properties and ecotoxicity values of these chemicals are compared and shown to be similar to those of 1,2-dimethyl-4-nitrobenzene. Therefore, all are expected to show similar chemical reactivity and biological activity.

Reliable data from acute fish toxicity tests on 1,2-dimethyl-4-nitrobenzene indicate low to moderate toxicity. The 7-day LC_{50} was 18 mg/L for the early life stage of *Brachydanio rerio*, while the 14-day LC_{50} for 3-4 week old guppies (*Poecilia reticulata*) was 9.3 mg/L. Although these exposure periods differ from the standard 96 hours, the measured values are similar to the 96-h LC_{50} value for fish of 16 mg/L calculated by ECOSAR.

A reliable acute oral toxicity test with rats on 1,2-dimethyl-4-nitrobenzene reported an LD_{50} of 2,636 mg/kg. In Ames tests, including tests conducted by the NTP, both 1,2-dimethyl-4-nitrobenzene and 2,4-dimethyl-1nitrobenzene produced positive results in some strains. An OECD 475, *in vitro* chromosomal aberration study for 2,4-dimethyl-1-nitrobenzene produced negative results. Mixed genotoxicity results are also summarized for the nitrotouenes.

No repeated dose toxicity data are available for 1,2-dimethyl-4-nitrobenzene. However, data exist for 2,4-dimethyl-1-nitrobenzene from a 6-week feeding study with rats, as well as for the nitrotoluenes from a comparative 13-week repeated dose study with rats and

mice. Clinical signs of toxicity in these studies included reduced food consumption and reduced weight gain. Increased liver and pancreas weight as well as hematological effects were observed for 2,4-dimethyl-1-nitrobenzene. Histological effects on the kidney, spleen and testis as well as impaired testicular function and increased estrus cycle in rats were observed for the nitrotoluenes.

While no developmental or reproductive toxicity data are available for 1,2-dimethyl-4-nitrobenzene, a combined developmental and reproductive toxicity screening for 3-nitrotoluene in rats found no developmental or reproductive toxicity. However, effects on blood and spleen were observed in the parental animals, along with less severe splenic effects in the offspring. An OECD 421, reproductive/developmental toxicity screening for 4-nitrotoluene in rats found no effects on insemination, fertility, or live birth indexes. Time to insemination and sex ratio of pups were also unaffected. Mean pup body weight was significantly reduced at the highest dose at which overt maternal toxicity was also observed.

It should also be noted that potential exposures to 1,2-dimethyl-4-nitrobenzene are expected to be extremely limited, since it is generated and used on site as a chemical intermediate and personal protective equipment is used during sampling events when any dermal contact might occur. Environmental exposures are expected to be extremely rare, since any spills would be handled in an appropriate manner to minimize release to the environment.

BASF Corporation's thoughtful use of existing data for 1,2-dimethyl-4-nitrobenzene and for its analogs 2,4-dimethyl-1-nitrobenzene and the nitrotoluenes, 2-nitrotoluene, 3-nitrotoluene, and 4-nitrotoluene is consistent with the HPV Challenge Program's goal of obtaining screening level hazard information, and this approach saves animals' lives by avoiding duplicative tests. Thank you for your attention to these comments. I may be reached at 610-586-3975, or via e-mail at josephm@peta.org.

Sincerely,

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Research & Investigations