This document was developed by NIEHS/NTP staff to facilitate internal and external review of a proposed research program prior to designing and conducting toxicology studies. The purpose of the research concept document is to outline the general elements of a research program that would address the specific public health concerns that prompted the nomination of the substance or issue for study. It may also encompass substance-specific studies that address larger public health issues or topics in toxicology. Additional information about the nomination, review, and selection of substances for study by the NTP is provided at ***Nominations to the NTP Testing Program*** (*http://ntp.niehs.nih.gov/go/nom*). A draft version of this research concept was reviewed by the NTP Board of Scientific Counselors at a public meeting on June 22, 2007 (*http://ntp.niehs.nih.gov/go/9741*), subsequently revised, and approved by the NTP Executive Committee.

NTP Research Concept: *o*-Phthalaldehyde

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Nomination Background and Rationale

o-Phthalaldehyde (OPA) was nominated by the National Institute for Occupational Safety and Health for toxicological characterization based on the limited availability of toxicological data and its increasing use as an alternative to glutaraldehyde in the sterilization of heat sensitive dental and medical equipment (http://ntp.niehs.nih.gov/go/29287).

OPA was approved by the U.S. FDA in 1999 for disinfecting medical devices and is marketed, sold, and used as a "safe" replacement for glutaraldehyde, which is a strong skin, eye, and respiratory irritant and has been demonstrated to cause sensitization and occupational asthma in humans. The compounds differ in molecular structure in that glutaraldehyde is a straight-chained hydrocarbon, whereas OPA is a benzene ring based structure. The safety of OPA relative to glutaraldehyde is largely based on its greater efficacy as a disinfectant, which allows for use at lower concentrations. There is no specific data or information indicating that OPA is a safe alternative to glutaraldehyde and neither OSHA nor the U.S. EPA have promulgated rules regarding safe exposure levels. There are virtually no peer-reviewed toxicological data in the literature for OPA. Both the U.S. EPA and U.S. FDA have received unpublished animal toxicity reports, which are protected as confidential business information. General summaries of these confidential reports have been made available, but these studies were not peer reviewed and specific details of the study design and the interpretation of the resultant data are not available. However, based on these summaries, information in the available Material Safety Data Sheet, and statements on the internet, it appears that OPA is not a developmental toxicant or mutagenic in bacterial tests, but it does induce chromosomal aberrations in mammalian cell assays and is moderately toxic in subchronic toxicological studies. While no published data are available for review, OPA has been noted as positive in the guinea pig maximization test and the mouse local lymph node assay. Consistent with this, a few human case reports indicate that OPA can cause mucous irritation, respiratory symptoms and IgE-mediated hypersensitivity reactions. These studies are limited in scope, but suggest that OPA may pose similar occupational hazards to those of glutaraldehyde. However, reviewable data are needed to define and document the potential hazard posed to healthcare workers handling OPA so that appropriate guidelines and protections can be put into place.

Key Issues

A major issue with respect to heath care worker exposure is the vapor pressure of OPA. It has been suggested that a benefit of OPA relative to glutaraldehyde is the lower required concentration and low vapor pressure of OPA. There are no published studies available for OPA vapor pressure. The measurement of vapor pressure and input from NIOSH regarding their specific data needs will be used to determine the appropriate route of exposure for subchronic toxicity studies. Prior NTP subchronic and chronic inhalation studies of glutaraldehyde will be used to allow comparisons between OPA and glutaraldehyde. However, additional glutaraldehyde studies may also be required. Further clarification will be required from NIOSH to determine the priority of these studies.

Proposed Approach

The overall goal of this research project is to investigate the potential for OPA to cause dermal and respiratory sensitization and systemic toxicity. The specific aims of the proposed studies are to:

- Assess dermal irritation and sensitization
- Evaluate respiratory sensitization and asthmagenic potential
- Evaluate dermal toxicity
- Obtain ADME data

The studies to assess irritation, sensitization, and asthmagenic potential are considered high priority studies within the framework of this research program for OPA and will include studies such as the mouse local lymph node assay and the mouse ear-swelling test. The dermal toxicity and ADME studies are considered secondary studies with a lower priority than the other proposed studies.

The OPA product typically used in health care settings is a solution containing a concentration of 0.56% OPA. An OPA concentrate is also available on the market containing 5.75% OPA. Test material concentrations for the proposed studies will likely be limited by OPA solubility, but doses should include these commercially available concentrations.

Significance and Expected Outcome

The use of OPA in health care settings is widespread and apparently increasing. It is reasonable to assume that more than 300,000 healthcare workers may be exposed to OPA. No other exposure information (including limits) is available. It is important to note that the FDA medical device approval process entails evaluation of the risk to patients of residues on disinfected medical devices, and the risk to users handling disinfectant solutions. According to published literature and adverse event reports submitted to the FDA, healthcare workers have experienced irritation of the eyes, skin, and nose and several patients have experienced anaphylaxis following procedures in which OPA was used to disinfect medical equipment. Although OPA has been suggested as a safer alternative to glutaraldehyde, there is an overwhelming lack of publicly available data on the safety of OPA. Based on information known regarding other aldehydes, including glutaraldehyde, there is a strong potential that *o*-phthalaldehyde may be a skin and respiratory sensitizer that may cause dermatitis with prolonged or repeated contact and may aggravate pre-existing bronchitis or asthma.

The data generated from this research program will complement NIOSH's proposed research plan to assess workplace practices, measure exposure concentration, develop monitoring methods, and perform immunological exposure assessments. Together these data will provide the basis for the determination of safe exposure limits for OPA and the development of guidance for protection of health care workers using OPA.

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