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The National Library of Medicine's (NLM) Hazardous Substances Data Bank (HSDB): Background, Recent Enhancements and Future Plans

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Abstract

The National Library of Medicine's (NLM) Division of Specialized Information Services (SIS) Toxicology and Environmental Health Information Program is responsible for the management of the online Hazardous Substances Data Bank (HSDB). HSDB, a part of NLM's Toxicology Data Network (TOXNET®), is a file of chemical/substance information with one record for each specific chemical or substance, or for a category of chemicals or substances. Like the rest of TOXNET's databases and other resources, HSDB is available online at no cost to global users. HSDB has approximately 5,600 chemicals and substances, with a focus on toxicology information and also on human exposure, industrial hygiene, emergency handling procedures, environmental fate, regulatory requirements, and related areas of likely interest to HSDB users. All data are from a core set of books, government documents, technical reports, selected primary journal literature, and other online sources of information, with a goal of linking the HSDB content to as much publicly available information as possible. HSDB's content is peer-reviewed by a Scientific Review Panel of experts covering the scope of HSDB content. Recent enhancements include the addition of chemical structures to HSDB records, the addition of new subfields such as age groups for human data, more occupational exposure standards, and the addition of information on numerous nanomaterials. Examples of future plans include providing more exposure-related information, e.g., uses of a chemical or substance in consumer products; the addition of information summaries aimed towards consumers and other members of the public wanting to learn about a chemical or substance; more visual content such as diagrams (images) of the pathways of metabolism of a substance; and enhanced search features and navigation.

Keywords

Information; Databases; Online; National Library of Medicine

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Conflict of interest

The authors declare that there are no conflicts of interest.

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1. Introduction

HSDB is available for free 24 hours a day (www.toxnet.nlm.nih.gov). It was established over forty years ago at NLM to assist the United States Agency for Toxic Substances and Disease Registry (ATSDR) and the United States Environmental Protection Agency (EPA) in collecting, documenting and making available online information about the chemical substances found at National Priority Listing Sites (NPL) throughout the United States. The initial selection, building and review of specific chemical records were accomplished via meetings of representatives from the three organizations. Chemicals found at NPL sites included pollutants such as heavy metals and their salts, biocides, herbicides, insecticides, radionuclides, solvents, gases and intermediates, complex mixtures and pharmaceutical preparations. The information placed into a chemical specific record was extracted from books, government documents, technical reports, selected primary journal literature, and other sources of online information.^{1, 2, 3}

HSDB's information has a broad scope, covering *Human Health Effects, Emergency Medical Treatment, Animal and Human and Ecotoxicity Excerpts, Metabolism/ Pharmacokinetics, Pharmacology, Environmental Fate/Exposure, Environmental Standards & Regulations, Chemical and Physical Properties, Manufacturing/Use Information, Laboratory Methods* (analytical and clinical determinations), *Synonyms and Formulations*, and *Safety Procedures*. HSDB data fields are also referred to as "data elements."

2. Chemical and substance selection

Chemicals, drugs, dietary supplements, venoms, heavy metals and other candidate compounds are evaluated and selected by the HSDB chemical selection team, an internal NLM group. Candidate chemicals are nominated by members of NLM's staff, the public, scientific and regulatory agencies, and advisory groups. Compounds that are the center of national and international news because of an accidental or intentional release or a report of being found in food, medications and drinking water supplies or an incident of adverse effects from newly approved pharmaceutical agents are also candidates for selection by NLM staff. The selection team utilizes a rationale for chemical selection which includes: level of toxicity; human, animal, plant and aquatic exposure; amount of production and use and related factors such as regulatory status in the United States and other countries. These are examples of chemicals and substances of interest that are evaluated for inclusion in HSDB, and also for updating of existing records if that judged to be needed based on new information and understanding that could be added:

- U.S. Consumer Product Safety Commission (CPSC, www.cpsc.gov) chemical-related consumer product recalls and other CPSC efforts (recent CPSC efforts on phthalates and nanomaterials are key examples);
- U.S. Drug Enforcement Agency (DEA, www.dea.gov) lists of scheduled chemicals and chemical intermediates used in manufacture of DEA regulated drugs of abuse;
- U.S. Department of Energy's (DOE, www.doe.gov) lists of radioactive and non-radioactive substances used at their production plants;

- U.S. National Institute of Environmental Health Sciences (NIEHS, <http://ntp.niehs.nih.gov/>) recent NIEHS and other U.S. Government agency efforts on nanomaterials are an example. Also, chemicals included in National Toxicology Program chemical reports;
- U.S. Department of Homeland Security (DHS, www.dhs.gov) “chemicals of interest” list; (examples include chemical warfare agents and their precursors);
- U.S. Environmental Protection Agency (EPA, www.epa.gov), such as:
 - Recent EPA and other U.S. Government agency efforts on isocyanates are a key example. Also, currently actively registered pesticides, restricted use and cancelled pesticide products banned from sale in the United States, herbicides and insecticides, high production volume chemicals, acutely toxic chemical substances, ambient and drinking water chemical contaminants, persistent chemical substances and drugs and chemicals in personal care products found in ambient and finished water supplies;
 - U. S. Food and Drug Administration (FDA, www.fda.gov) drugs currently approved in the U.S. and drugs removed from both U.S. and other international markets, drug black box warnings and cosmetic and food colorant lists along with excipients used in manufacture of food, drugs, cosmetics other consumer products;
 - U.S. National Institute of Occupational Safety and Health (NIOSH, www.cdc.gov/niosh) and U.S. Occupational Safety & Health Administration (OSHA, www.osha.gov). Chemical substances that are workplace contaminants and hazards include toxic industrial chemicals (TICs),

Non-U.S. governmental organizations which provide chemical and substance candidates for HSDB include but are not limited to the following: International Agency for the Research on Cancer (IARC, www.iarc.fr) and World Health Organization (WHO, www.who.int) (via their monographs on chemicals, drugs and biological products and International Programme on Chemical Safety (IPCS), European Chemicals Agency (ECHA, <http://echa.europa.eu/>) and other advisory groups and review panels, and industry groups representing cosmetics, excipients, flavorings, dyes and perfumes.

3. Data quality tags

The content found in HSDB records is labeled with data quality tags. While not a new feature, these tags provide users with a good indication of the level of scientific review which the records have undergone. *PEER REVIEWED* tags indicate that the data has been evaluated by NLM’s Scientific Review Panel (SRP) which is a group of outside NLM advisors who have extensive education and knowledge of chemistry, industrial hygiene, pharmacology, animal and human toxicology, atmospheric and aquatic and terrestrial fate, occupational and emergency medicine, radiobiology and related subjects. The SRP meets three times a year and examines about 350 HSDB records per year. *QC* (Quality Control) *REVIEWED* tags indicate that the data was excerpted from an original source and has been

excerpted as is. An HSDB senior reviewer or an SRP subcommittee conducts a quality control review while a full peer review is pending. QC review may be utilized to expedite releasing information to the public. *UNREVIEWED* tags, signify that the data has not been evaluated for scientific accuracy and only excerpted as is from the source. As a general rule, public HSDB records do not include *UNREVIEWED* tags. These tags are utilized as part of the internal record building process unless there is a special circumstance.

4. Examples of recent enhancements

4.1 Ecotoxicity data element

A new data element was created to collect information on the potential ecotoxicity of a chemical. This includes effects on biomass, population density, mortality, morbidity and effects on microbial and aquatic and terrestrial populations of endemic species. Data found in the *Ecotoxicity Excerpts* is taken from abstracts of primary literature, governmental and non-governmental reports and data from texts.

4.2 Other standards, regulations, and guidelines data element

The Other Standards Regulations and Guidelines (OSRG) data element replaced a previous occupational data element. The OSRG element allows for expanded information from the United States and international organizations that may affect the U.S. Examples of expanded information sources include: Emergency Response Planning Guidelines (ERPGs) from the American Industrial Hygiene Association (AIHA), the Chemical Weapons Convention (CWC) international treaty and the European Commission (EC), International Uniform Chemical Information Database (IUCLID).

4.3 Subheadings used in HSDB data extraction

Because of the large amount of information appearing in certain HSDB data elements, it was determined that the undifferentiated narrative format which had been used previously required some degree of categorization to be of optimum use.

Two major data elements located within HSDB are the *Human* and *Non-Human Toxicity Excerpts*. In the *Human Toxicity Excerpts* data element, the following subheadings were created to more efficiently locate specific data:

- *Human Exposure Studies* - Controlled studies conducted on humans in a laboratory setting and include dermal sensitization tests. Exposure is measured, not controlled, and human biological effects are reported.
- *Signs and Symptoms* - Specific statements describing the signs or symptoms of chemical exposure.
- *Case Reports* - Exposure of a subject or subjects to the chemical, either accidentally or intentionally, with description of adverse events and treatment outcomes. Case Reports do not contain information on control subjects.
 - When data indicate, pediatric specific subheadings have been added to case reports in the Human Health Effects section. Although these pediatric

subheadings are most often found under case reports, they may appear elsewhere in the record such as the Metabolism/Pharmacokinetics section. Examples include: infant, premature; infant, newborn; child; child, preschool; adolescent.

- *Surveillance* - A measure of chemical exposure including detailed information on specific medical tests to determine the impact on cardiac, hepatic, neurological or respiratory functions and potentially serious medical conditions. Information from poison control center data is also provided.
- *Epidemiology Studies* – Evaluation of the potential of a chemical to induce adverse effects on a specific group of exposed individuals compared to a control study group. Study designs include case control studies, cohort studies and meta-analysis. Biochemical or molecular epidemiologic studies that incorporate laboratory methods in analytical investigations are included. Other information may include descriptive studies examining differences in disease rates among populations in relation to age, gender, race, and differences in temporal or environmental conditions.
- *Alternative and In Vitro Tests* - Studies of interest that are not covered under *Genotoxicity* or endocrine modulation. For example, studies conducted using a human cell line.
- *Genotoxicity* - Studies that use in vitro and in vivo methods involving human tissues/cells to determine a genotoxic response (includes positive and negative studies).
- *Biomonitoring* - Studies that correlate the results of biological monitoring with exposures. Includes studies that, for example, show blood lead level concentrations or metabolites from organic chemical exposure and indications of raised levels of carbon monoxide in blood samples.
- *Endocrine Modulation* - Effects of exogenous chemicals that alter the synthesis, secretion, transport, binding, elimination and action of natural hormones in the body which are responsible for homeostasis, reproduction, development and behavior.

In the *Non-human Toxicity Excerpts* data element, the following subheadings were created:
Laboratory Animals

- *Acute Exposure* - Studies conducted in animals for up to five days in duration.
- *Subchronic or Prechronic Exposure* - General study designs exposing animals to a chemical for six days to six months.
- *Chronic Exposure or Carcinogenicity* - General study design that exposed animals for over six months and all carcinogenicity studies regardless of the length of exposure to a chemical carcinogen.
- *Neurotoxicity* - Studies designed to look at neurotoxicity as an endpoint. These might include delayed occurrences of neurotoxicity.

- *Developmental Neurotoxicology* - Adverse effects induced during pregnancy or as a result of parental exposure that can manifest as neurotoxicity at any point in the life span of the offspring.
- *Behavioral Studies* - Objective study of animal behavior following exposure to a chemical substance.
- *Alternative and In Vitro Tests* - In vitro studies of interest not covered under endocrine modulation. It covers all tests validated by ICCVAM and its European counterpart.
- *Genotoxicity* - All genotoxicity tests regardless of the species/microorganism used except those conducted with a human cell line, for example, Salmonella typhimurium and in vivo micronucleus assay in mice.
- *Endocrine Modulation* - Exogenous agents that alter the synthesis, secretion, transport, binding, action or elimination of natural hormones in the body which are responsible for the maintenance or homeostasis, reproduction, development and or behavior.
- *Veterinary Case Reports* - Domestic animal poisonings, whether in the field or a household, for example, the accidental ingestion of antifreeze liquid by cats and dogs.

In the *Ecotoxicity Excerpts* data element, the following subheadings were created:

- *Birds and Mammals* - All wild birds and mammals affected by the chemical except for animals being raised for food. Studies are conducted both in the field and laboratory.
- *Aquatic Species* - Fish, algae, or protozoans affected by the chemical in the natural environment. Studies are conducted in the field and laboratory.
- *Other Terrestrial Species* - Effects of a chemical on non-target invertebrate insects or vertebrates not covered under *Birds and Mammals* such as snakes and other reptiles that are commonly used to determine the effects of the chemical in the environment.
- *Field Studies* - Ecological assessments of biological organization and populations, communities and ecosystems studies conducted to assess the adverse effect of a chemical substance.
- *Accidental Poisonings* - Applies to wildlife and covers events like fish kills which may be accidental or intentional.

5. Other significant enhancements to HSDB

5.1 Nanomaterials

The use of nanomaterials in consumer products such as clothing, building materials, electronics, medical instruments and medical treatment modalities has been of global interest to consumers, scientists, regulatory agencies, industry, and others. NLM examined a wide range of sources of information and developed records for the following

nanomaterials: silver nanoparticles, iron nanoparticles, zinc oxide nanoparticles, cerium oxide nanoparticles, carbon nanotubes, titanium oxide nanoparticles, and fullerenes. These nanotechnology products were added to HSDB in 2009. More recently, records were added in 2012 for gold nanoparticles and platinum nanoparticles. All nanomaterial records include information concerning use, chemical and physical properties, human and non-human toxicology, and environmental fate.

Nanomaterial information, such as the HSDB records, is critical for stakeholders to acquire essential knowledge to address health and ecological implications. The U.S. Environmental Protection Agency (EPA) is working in the field of nanomaterials including conducting environmental assessments and publishing case studies³. The current HSDB records cover two major types of nanomaterials: carbon-based and metal-based. The recent addition of nanomaterial information to HSDB is, in part, an effort to continue the NLM function of serving as a national information resource and supporting biomedical research.

5.2 North American Poisonous Scorpion/Spider/Snake Venoms

Bites from scorpions, snakes and spiders occur throughout the world. Some bites are harmless while others cause severe morbidity and mortality. New HSDB records were built for several North American venomous animals: North American Agkistrodon (Snake Venoms) which includes copperheads and water moccasins (cottonmouth snakes); North American Centruroides (Black Scorpion Venom); North American Loxosceles (Recluse Spider Venom) and North American Latrodectus (Widow Spider Venom).

6. Future enhancements to HSDB

Following a needs assessment completed in 2012, the HSDB team is planning future enhancements to the database. The team has implemented initial enhancements and these efforts will continue. The enhancements will focus on expanding content, improving user experience, expanding user audience, and increasing speed of information delivery. Also, a major focus will be in adding visual content such as diagrams (images) of the pathways of metabolism of a substance, photos or drawings of an animal or plant associated with a substance, and pictograms and label information required under the newly implemented Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

HSDB will also be enhanced with Scorpion, Snake and Spider antivenom antidotes and the addition of venoms from scorpions, snakes and spiders of other North American, Central American and South American venomous organisms, along with European, African, Asian and Australian organisms of interest. In addition, vaccines, both commercially available monovalent and polyvalent types, will also be added. Further, new nanomaterials and other chemicals and substances will be added, along with selective updating and enhancement of the contents of records for current chemicals and substances. For example, nanomaterials have been the focus of very active research efforts in recent years, resulting in numerous new publications to consider for addition to HSDB records.

Abbreviations

ATSDR	Agency for Toxic Substances and Disease Registry
CPSC	Consumer Product Safety Commission
DEA	Drug Enforcement Agency
DHS	Department of Homeland Security
EPA	Environmental Protection Agency
ECHA	European Chemicals Agency
FDA	Food and Drug Administration
HSDB	Hazardous Substances Data Bank
IARC	International Agency for the Research on Cancer
IPCS	International Programme on Chemical Safety
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute of Occupational Safety and Health
NLM	National Library of Medicine
OSHA	Occupational Safety & Health Administration
QC	Quality Control
TICs	toxic industrial chemicals
TOXNET[®]	Toxicology Data Network
WHO	World Health Organization

References

1. National Library of Medicine. [accessed July 2, 2014] Toxicology and Environmental Health Information Program (TEHIP) Fact Sheet. <http://www.nlm.nih.gov/pubs/factsheets/tehipfs.html>
2. Recorded videocast of the May 6, 2009 Hazardous Substances Data Bank Symposium, part of the commemoration of the 75th meeting of the HSDB Scientific Review Panel (SRP); http://www.nlm.nih.gov/pubs/techbull/mj09/mj09_sis_reprint_videocast.html
3. National Library of Medicine. [accessed July 2, 2014 7/1/2014 02/21/2013] Hazardous Substances Data Bank (HSDB) Fact Sheet. www.nlm.nih.gov/pubs/factsheets/hsdbfs/html

Figure 1.
Human Toxicity Excerpts

Methyl t-butyl ether

CASRN: 1634-04-4

Non-Human Toxicity Excerpts:

/LABORATORY ANIMALS: Acute Exposure/ Six groups of 10 Charles River COBS albino rats (5 males and 5 females) were exposed to methyl tert-butyl ether (MTBE) vapor concentrations of 44, 65, 86, 99, 167, and 395 mg/L (12,200, 18,000, 23,800, 27,400, 46,200, and 109,200 ppm) for a single exposure period of 4 hr. Rats were subsequently observed for 14 days. Symptoms from MTBE exposure included hyperactivity, lacrimation, ataxia, tremors, clonia, and unconsciousness. No effects on body weight were noted during the 14 day observation period. Mild to minimal lung hyperemia was noted in rats surviving to 14 days.

[European Commission, ESIS; IUCLID Dataset, tert-Butyl methyl ether (1634-04-4) p.81 (2000 CD-ROM edition). Available from, as of September 27, 2010: <http://esis.jrc.ec.europa.eu/> **PEER REVIEWED**

/LABORATORY ANIMALS: Acute Exposure/ Ten Sprague Dawley rats (5 male, 5 female) received application of 2000 mg/kg undiluted methyl tert-butyl ether (MTBE) to shaved unbraded skin. Application area was about 6x5 cm (approx 10% of body area). MTBE was held in contact with the dorsal area by an occlusive patch (gauze + aluminum strip) for 24 hr. Subsequently rats were observed for 14 days. Observation was carried out at 30 min, 2, 4, and 6 hr on the first day after the administration and then twice a day up to the end of the observation period. No animals died. No general clinical signs nor behavioral alterations were observed in any treated animal. Slight erythema was observed at the application site in 4/10 animals. Body weight gain was considered within normal limits. Postmortem examination revealed no appreciable macroscopic findings. Histological examination was not performed.

[European Commission, ESIS; IUCLID Dataset, tert-Butyl methyl ether (1634-04-4) pp.86-7 (2000 CD-ROM edition). Available from, as of September 27, 2010: <http://esis.jrc.ec.europa.eu/> **PEER REVIEWED**

/LABORATORY ANIMALS: Acute Exposure/ Two Macacus rhesus monkeys (1 male, 1 female) were exposed to methyl tert-butyl ether (MTBE) by inhalation for 5 days, 6 hr/day, dosage 12,400 - 341,000 mg/cu m. 12,400 and 17,400 mg/cu m for 6 hr, no symptoms; from 30,200 mg/cu, ataxia; from 68,400 mg/cu m, emesis, prostration, unconsciousness; from 110,000 mg/cu m, tremor, bradypnia; from 341,000 mg/cu m, apnea after 85 min.

[European Commission, ESIS; IUCLID Dataset, tert-Butyl methyl ether (1634-04-4) p.132 (2000 CD-ROM edition). Available from, as of September 27, 2010: <http://esis.jrc.ec.europa.eu/> **PEER REVIEWED**

Figure 2.
Non-Human Toxicity Excerpts

CHLOROBENZENE

CASRN: 108-90-7

Ecotoxicity Excerpts:

/AQUATIC SPECIES/ Chlorobenzene was less hepatotoxic to trout than rats. This difference could not be totally accounted for by reduced absorption in trout. ... Glutathione concentrations in trout livers were 1/3 of those of the rat and prior depletion of the tripeptide /glutathione/ led to irreversible binding of chlorobenzene to trout liver protein; equivalent to that of rats suffering extensive liver necrosis. No consistent correlation between glutathione content or protein binding and liver damage was seen in either species.

[Dalich GM, Larson RE; Comp Biochem Physiol 80 (1): 115-22 (1985)] **PEER REVIEWED**

/AQUATIC SPECIES/ Four chlorobenzenes (chlorobenzene, 1,3-dichlorobenzene, 1,4-dichlorobenzene, p-chloro-methylbenzene) were administered to the crucian carps (*Carassius auratus*) by peritoneal injections in the laboratory for 30 days. Serum testosterone and 17 beta-estradiol concentrations were detected using radioimmunoassay (RIA), and the activities of two hepatic microsome enzymes, glutathione s-transferase (GST) and UDP-glucuronosyltransferase (UDPGT), were measured using the modified methods as described by Habig and Owens. Results showed that the four chlorobenzenes caused significant increases in serum testosterone concentration in the crucian carps ($P < 0.05$) compared to the controls, but they caused no significant effect on 17 beta-estradiol level. All test chemicals caused a change in hepatic GST activity in crucian carps, with significant increases in enzyme activity ($P < 0.05$). Chlorobenzene, 1,3-dichlorobenzene and p-chloro-methylbenzene resulted in a marked inhibition to UDPGT activity in crucian carp ($P < 0.05$) except 1,4-dichlorobenzene. The changes in hepatic microsome enzyme activities may have resulted in the alterations of serum sex steroids levels in the crucian carps.

[Qian Y et al; Chemosphere 57 (2): 127-33 (2004)] **PEER REVIEWED** PubMed Abstract

/PLANTS/ This study investigates the effects of chlorobenzenes on the diatom *Cyclotella meneghiniana* using DNA measurement as a toxicity parameter and related toxicity to different physicochemical properties of chlorobenzenes. The organisms were exposed to chlorobenzene solutions for 48 hr to obtain effective concentration (EC50) values (in terms of percent DNA reduction). The toxicity (EC50) increased with increasing degree of chlorination, as follows: monochlorobenzene (235.74 mg/L), dichlorobenzenes (23.33-51.88 mg/L), trichlorobenzenes 0.59-6.42 mg/L, tetrachlorobenzenes (0.27-1.39 mg/L), pentachlorobenzene (0.008 mg/L) and hexachlorobenzene (0.002 mg/L). Quantitative structure-activity relationships were developed showing high correlations, as follows: water solubility ($r^2 = 0.96$); molecular volume ($r^2 = 0.92$); zero-order connectivity index ($r^2 = 0.92$); second-order connectivity index ($r^2 = 0.02$); molecular surface area ($r^2 = 0.92$); octanol/water partition coefficients ($r^2 = 0.86$); bioconcentration factor ($r^2 = 0.86$); and inorganic/organic character ($r^2 = 0.83$). A poor correlation, however, was obtained with the molecular negentropy index ($r^2 = 0.25$). The toxic effect (EC50) was explained in terms of a partitioning process as a function of the aqueous solubility of the chlorobenzenes and was found to occur at similar degrees of exposure saturation.

[Figueroa I DC, Simmons MS; Environ Toxicol Chem 10 (3): 323-30 (1991)] **PEER REVIEWED**

Figure 3.
Ecotoxicity Excerpts

SILVER NANOPARTICLES

CASRN: NO CAS RN

Human Health Effects:**Toxicity Summary:**

IDENTIFICATION AND USE: Products utilizing the antimicrobial properties of silver (Ag) nanoparticles range from surgical tool coatings, wound dressings, surface and personal sanitizing sprays, toothbrushes, home purification systems, food storage containers, socks and infant pacifiers. HUMAN EXPOSURE AND TOXICITY: A prospective, single-center, open-label study of 30 patients with relatively small burns that required skin grafting was conducted. Serum silver levels were measured before, during and at discontinuation of the use of the Acticoat dressings, and again at 3 and 6 months following completion of treatment. The median total postoperative wound size was 12% of the total body surface area. The median time to maximum silver levels was 9 days. The median maximum serum silver level was 56.8 ug/L. The median serum level at 6 months was 0.8 ug/L. There were no hematological or biochemical indicators of toxicity associated with the silver absorption observed in this study. Exposure to **silver nanoparticles** among the general population may be via dermal contact and ingestion by those administered this substance in nanoparticle-enhanced antimicrobial drugs. Occupational exposure to nanoparticles may occur through inhalation of dust and dermal contact with these compounds at workplaces where nanoparticles are produced or used. Nanomaterials are currently incorporated into many consumer products. Due to the consequence of widespread usage and the supposed persistence against degradation, human and environmental exposure to nanomaterials are likely to increase. ANIMAL STUDIES: A study tested the oral toxicity of **silver nanoparticles** (60 nm) over a period of 28 days in rats. Eight week old rats were divided into four 4 groups: vehicle control, low-dose group (30 mg/kg), middle-dose group (300 mg/kg), and high-dose group (1000 mg/kg). After 28 days of exposure, the blood biochemistry and hematology were investigated, along with a histopathological examination and silver distribution study. The male and female rats did not show any significant changes in body weight relative to the doses of **silver nanoparticles** during the 28-day experiment. However, some significant dose-dependent changes were found in the alkaline phosphatase and cholesterol values in either the male or female rats, seeming to indicate that exposure to over more than 300 mg of **silver nanoparticles** may result in slight liver damage. The tissue distribution of silver nanoparticles did show a dose-dependent accumulation of silver content in all the tissues examined. In particular, a gender-related difference in the accumulation of silver was noted in the kidneys, with a twofold increase in the female kidneys when compared with the male kidneys. A study attempted to investigate the inflammatory responses and pulmonary function changes in rats during 90 days of inhalation exposure to **silver nanoparticles**. The rats were exposed to **silver nanoparticles** (18 nm diameter) at concentrations of 0.7×10^6 particles/cu cm (low dose), 1.4×10^6 particles /cu cm (middle dose), and 2.9×10^6 particles /cu cm (high dose) for 6 hr/day in an inhalation chamber for 90 days. The lung function was measured every week after the daily exposure, and the animals sacrificed after the 90-day exposure period. Cellular differential counts and inflammatory measurements, such as albumin, lactate dehydrogenase (LDH), and total protein, were also monitored in the acellular bronchoalveolar lavage (BAL) fluid of the rats exposed to the **silver nanoparticles** for 90 days. Among the lung function test measurements, the tidal volume and minute volume showed a statistically significant decrease during the 90 days of silver nanoparticle exposure. Although no statistically significant differences were found in the cellular differential counts, the inflammation measurements increased in the high-dose female rats. Meanwhile, histopathological examinations indicated dose-dependent increases in lesions related to silver nanoparticle exposure, such as infiltrate mixed cell chronic alveolar inflammation, including thickened alveolar walls, and small granulomatous lesions. Therefore, when taken together, the decreases in the tidal volume and minute volume and other inflammatory responses after prolonged exposure to **silver nanoparticles** would seem to indicate that nanosized particle inhalation exposure can induce lung function changes, along with inflammation, at much lower mass dose concentrations when compared to submicrometer particles. A study was undertaken to examine the DNA damage response to polysaccharide surface functionalized (coated) and non-functionalized (uncoated) Ag NPs in two types of mammalian cells; mouse embryonic stem (mES) cells and mouse embryonic fibroblasts (MEF). Both types of Ag NPs up-regulated the cell cycle checkpoint protein p53 and DNA damage repair proteins Rad51 and phosphorylated-H2AX expression. Furthermore both of them induced cell death as measured by the annexin V protein expression and MTT assay. The observations also suggested that the different surface chemistry of Ag NPs induce different DNA damage response: coated Ag NPs exhibited more severe damage than uncoated Ag NPs. The results suggest that polysaccharide coated particles are more individually distributed while agglomeration of the uncoated particles limits the surface area availability and access to membrane bound organelles.

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Figure 4.
Example of a nanomaterial record

North American *Loxosceles* (Recluse Spider Venom)

CASRN: NO CAS RN

Human Health Effects:

Toxicity Summary:

The most definitive physical feature of recluse spiders is their eyes: most spiders have eight eyes that typically are arranged in two rows of four, but recluse spiders have six equal-sized eyes arranged in three pairs, called dyads. There is a dyad at the front of the cephalothorax (the first main body part to which the legs attach) and another dyad on each side further back with a space separating the dyads from one another. Many publications refer to the violin marking on the dorsal (top) surface of the cephalothorax (head region) as the most important diagnostic feature. Although this marking is fairly consistent in mature brown recluses and Texan recluses (*Loxosceles* *devia*), it can vary in intensity and sometimes fades in preservative, and it is very faint to nonexistent in several recluse species found in the southwestern United States (e.g., the desert recluse, *Loxosceles* *deserta*). Therefore, checking the eye pattern is the best way to eliminate almost all suspect nonrecluse spiders from consideration whereas the presence or absence of the violin marking may lead to misidentifications. Non-arachnologists (including physicians) have a strong tendency to see "violins" on all body surfaces of harmless spiders and incorrectly assume that they have properly identified a brown recluse spider. In addition, the abdomens of all North American recluses are covered with fine hairs and are uniformly colored, although the coloration can vary from light tan to dark brown, depending in part on what they have eaten recently. There is never a coloration pattern on the abdomen of North American specimens. Finally, the uniformly colored legs are similarly covered with fine hairs whereas many nonrecluse spiders have stout spines and/or stripes, rings, or spots on their legs. Some other spiders share each of these physical characteristics. However, to be identified as a recluse spider, it must have all five of these characteristics: 1. six eyes in dyads (pairs) 2. uniformly colored abdomen with fine hairs 3. no spines on the legs 4. uniformly colored legs 5. body not more than 3/8" in length. ... Eleven species of recluse spiders are native to the United States and two non-natives have become established in certain highly restricted areas of the country. The brown recluse spider is the proper common name for only one species, *Loxosceles* *reclusa*. It is the most widespread of the North American recluse spiders and lives in the south central Midwest from Nebraska to Ohio and south through Texas to Georgia. Although the brown recluse does not live in California, we do have four species of native recluse spiders. The most common Californian recluse spider is the desert recluse, *Loxosceles* *deserta*. It is found mostly in the Sonoran and Mojave deserts, in the foothills of the lower San Joaquin Valley, and in adjacent areas of Mexico; most of these areas are sparsely populated by humans. In older literature, this spider was referred to as *Loxosceles* *unicolor*. There are additional species (*Loxosceles* *russelli*, *Loxosceles* *palma*, *Loxosceles* *martha*), but they are so uncommon that they are of scientific interest only. Recluse spiders, as their name implies, are reclusive. These nocturnal spiders emerge from their retreats at night and actively hunt down prey or may wait for prey to land in the small area several inches from their retreat. Although they do not build webs to capture prey, they do use silk to build a retreat in which they hide during the day. As dawn approaches, they may seek shelter in dark places such as in clothing or shoes. Also, mature males roam in search of females. It is these two behaviors that can bring them into contact with people. In nature, recluses are found in cracks and crevices in and under rocks. Recluses have very much benefited from human-altered environments where they are readily found under trash cans, plywood, tarps, or rubber tires, in boxes, etc. They are synanthropic (found in association with humans) and therefore are considered "house" spiders. In fact, in South America the recluse species have common names that translate as "the spider behind the picture" or "the spider in the corner." Recluse spiders are relatively long lived. Among the various species, they mature after about 1 year and average a 2- to 4-year life span with some living more than 7 years under laboratory conditions. They are also well known for surviving long periods (6-12 months) without food before perishing. [University of California Agriculture and Natural Resources; Statewide Integrated Pest Management Program (UC IPM on-line); Brown Recluse and Other Recluse Spiders (Last revised January 2008). Available from, as of July 16, 2012: <http://www.ipm.ucdavis.edu/PMG/PESTNOTES/pn7468.html> **PEER REVIEWED**

Figure 5.
Example of a snake or spider record