CCOHS

Substance *of*

Interesting chemical facts from the creators of the CHEMINFO database

*Excerpts from Liaison, our quarterly user newsletter*

# Evidence-based Health Hazard Evaluations
# The CHEMINFO Story

An "evidence-based" approach is the process of systematically finding, critically evaluating and interpreting the best available literature and research findings as the basis for decisions. As a result, better decisions are made. Within the context of evaluating the potential health hazards of a chemical, the questions posed can be broad, ranging from skin and eye irritation to carcinogenicity. Over the past several years, CCOHS has developed an evidence-based system, which is applied when assessing the potential health hazards of chemicals reviewed in its CHEMINFO database, a comprehensive source of health and safety information on chemicals.

*We begin with a discussion of the key sources of information that CCOHS researchers routinely consult, and introduce the search process.*

## Chapter One: Sources of Health Hazard Information

The identification and selection of quality information is a crucial first step in assessing the potential health hazards of a chemical. In every case, it is necessary to conduct a systematic search of the toxicological literature. This task can be a daunting one, because it is "feast" or "famine", or anything in between. For example, a recent TOXLINE® search for information on "carbon monoxide" (CAS No. 630-08-0) retrieved over 10,000 hits, compared to one for "sodium lauryl trioxyethylene sulfate" (CAS No. 13150-00-0), which uncovered less than 20! Results can include animal toxicity studies, human case reports, epidemiological studies, and reviews. When the results are overwhelming, it is necessary to sift through a tidal wave of journal articles, books, and unpublished literature. However, on the other hand, a lack of results can certainly provide its own issues.

Each CHEMINFO review is produced following an extensive consultation of the available literature. Direct information/full text resources (e.g. RTECS® database, books and monographs), and bibliographic databases, searchable collections of toxicology references (e.g. TOXLINE®), are scrutinized for relevant information. Chemical directory databases (e.g. CHEMINDEX) are consulted to obtain identification parameters (e.g. chemical synonyms, structures), regulatory list information and links to specific databases where additional information can be found. In addition, CHEMINFO staff routinely conduct supplementary manual searches of the current issues of over 40 occupational toxicology journals. This "current awareness" exercise ensures that the most recent research available at the time of a review is included.

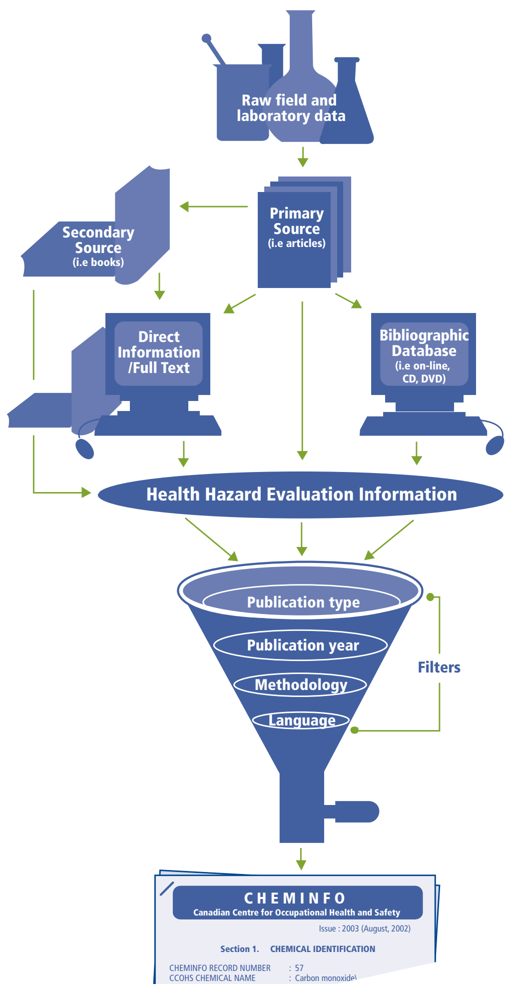


**Figure 1: Flow of Hazard Evaluation Information**

CHEMINFO specialists rely almost exclusively on primary literature, when available, to draw independent, verifiable conclusions on the potential health hazards of a chemical. Primary sources are original research papers written by the scientists who actually conducted the research. This literature is preferred because secondary sources can:

- Simply transmit the written conclusions of a primary source without evaluating the credibility of the study design. When you use a primary source you can see how the conclusions were reached.
- Apply different standards for data analysis and interpretation, which can lead to very different conclusions than would be arrived at by applying legislated regulatory criteria, e.g. the Controlled Products Regulations (WHMIS) or the OSHA Hazard Communication Standard.
- Inadvertently introduce errors in transcription (e.g. improper definition of the chemical, or the incorrect use of units, such as mg/kg instead of g/kg)

Nevertheless, secondary sources can prove useful in the search for relevant primary source materials, which may not be included in newer sources or bibliographic databases.

The key sources used to develop the potential health effects and toxicological information sections of CHEMINFO are outlined in Table 1. This list is not exhaustive, but highlights sources that have been carefully selected by CCOHS occupational health and safety specialists for their relevancy, validity, accuracy and/or timeliness.

To help visualize our procedures for researching a CHEMINFO review, imagine fluid being passed through a funnel. In this funnel, there are a series of filters (see Figure 1). The fluid represents the "content" part of the CHEMINFO literature search. Before the fluid is poured into the funnel, a preliminary search of the literature is carried out to determine the volume of literature available on a chemical. If the volume of information retrieved exceeds the capacity of the funnel, it becomes necessary to re-evaluate the search strategy. Techniques for refining a search strategy will be discussed in upcoming chapters of this series.

At the top, the funnel is wide. Many pieces of information can fit though this opening, and thus only the most obviously irrelevant results are excluded. For example, duplicates and references that do not focus on the chemical of interest, are identified and discarded. As the information flow travels through the funnel, it passes through a series of filters. The sieves can be modified to limit articles to a certain set of criteria, including publication type, publication year, language, and/or study methodology. These filters screen the search results, to leave a concentrated set of key original articles. This is the information that is carefully reviewed, evaluated and summarized in the preparation of the human health and toxicity sections of CHEMINFO.

*Chapter 2 continues the CHEMINFO Story by outlining techniques for conducting comprehensive searches in bibliographic databases.*

## Chapter Two: Searching Bibliographic Databases – An Exhaustive Search

Bibliographic databases provide descriptive information about literature citations including:

- name of the author(s)
- title of the document
- name of publisher or source
- usually an abstract or summary
- descriptors or keywords

These databases contain references to different types of literature such as journal articles, research reports, published and unpublished papers, conference proceedings, and textbooks. While they do not actually store the text of the document itself, bibliographic databases are important tools for locating references about a specific topic/issue, and for keeping up-to-date with recent developments in a particular area of interest.

The key starting point for the CHEMINFO team's detailed review of a chemical is an exhaustive search of selected bibliographic databases relevant to the field of occupational toxicology.

No single database is all-inclusive in its coverage of published research. Each differs in the number and extent of journals and references indexed, and in the keyword system used. Therefore, more than one database is consulted in order to ensure that nothing important is overlooked. Databases searched on a regular basis include:

**TOXLINE** - contains over 1,500,000 references from 1980 to present. Includes an extensive collection of references related to the biochemical, pharmacological, physiological, and toxicological effects of chemicals from the National Library of Medicine (NLM).

**OSHLINE™ with NIOSHTIC®/NIOSHTIC-2** - contains over 225,000 references spanning over 100 years. NIOSHTIC® was compiled by the U.S. National Institute for Occupational Safety and Health (NIOSH), and is an important source of historical information. OSHLINE™ is compiled by CCOHS, and continues the coverage by NIOSHTIC®, to provide up-to-date coverage of international occupational health and safety research literature from 1998 to the present.

Both TOXLINE and OSHLINE™ with NIOSHTIC®/ NIOSHTIC-2 are available from CCOHS.

### Steps in developing a search strategy

Retrieval of relevant information from bibliographic databases can sometimes prove challenging. An inappropriate search strategy may lead to missing important studies (low sensitivity), or retrieving many citations of studies that are not applicable (low specificity and low precision). Therefore, a carefully designed plan of attack is critical to the efficient identification of relevant information.

The main steps involved in locating relevant toxicological literature from bibliographic databases are described below.

***Step 1: Identify substance/agent***

The fundamental first search step is to determine accurate chemical identifiers such as the chemical name, synonyms, and the various registry numbers assigned to the chemical (e.g. RTECS, EINECS, NIOSH). The most important registry number is the Chemical Abstract Service (CAS) Registry Number, which is considered the universal "authority" for identifying compounds. CAS Numbers allow for the unambiguous identification of compounds by structure, composition, and other properties.

An excellent source of this type of information is CCOHS's CHEMINDEX, a chemical directory database that contains key identification parameters for over 260,000 substances. It is available for free online at: ccinfoweb.ccohs.ca/ chemindex/search.html. CHEMINDEX also functions as a "pointer" database, because it identifies which CCOHS database(s) contain information on the substance. Another useful "identification" source is CHEMIDplus (also available free online at: chem.sis.nlm.nih.gov/c hemidplus/) from the National Library of Medicine (NLM).

A good example of the importance of proper identification arose recently during a search for information on the chemical propylene glycol monomethyl ether. "Propylene glycol monomethyl ether" is a non-specific name for the commercial product (CAS Number 1320-67-8 or 28677-93-2), which is composed of a mixture of two isomeric forms: alpha (1-methoxy-2-propanol, CAS Number 107-98-2), and beta (2-methoxy-1-propanol, CAS Number 1589-47-5). Since the alpha isomer is favoured during preparation, and thus constitutes the bulk of the end product, this isomer is also loosely referred to as "propylene glycol monomethyl ether" by much of the literature. Given that the alpha and beta isomers differ in toxicity, it is essential to determine the composition of the mixture, and distinguish between the individual isomers. In this case, it was extremely important to precisely identify specific synonyms and CAS Numbers for the chemical or isomer of interest.

***Step 2: Prepare initial search strategy***

Once the relevant identification parameters for a chemical have been located, these terms can be combined into a single, comprehensive search statement (using the Boolean operator "OR"). While it may seem complicated to do so, searching on these terms separately will result in duplication within and between databases, and in the end, you will end up having to review more search results than is necessary.

Due to the imprecise and complex nature of the synonyms and trade names that can be used to identify a single substance, searching by the CAS Registry Number is by far the most accurate and efficient. Use of the CAS number eliminates the need to predict the formatting and nomenclature for a synonym that was used by the author or information provider. However, restricting your search to only the CAS Registry Number for a chemical will omit a significant number of references from which the CAS Numbers are missing, miscoded, or not systematically used. Therefore, it is necessary to incorporate a search on selected synonyms and, sometimes trade names or proprietary names, to ensure the best search results.

Obviously, including all possible terms for a substance will yield the greatest number of results. For example, a search for information about isopropylamine that incorporates only one of its chemical names would overlook documents that refer to this chemical by other synonyms such as 2-aminopropane, or MIPA. Variations in spelling, word endings (e.g. plural versus singular) must also be considered. The desired comprehensiveness of the results will dictate how extensive the list of synonyms needs to be.

*Step 3: Conduct preliminary search*

It is best to begin with a broad preliminary search, rather than a very narrow one, because it is more effective to later refine a comprehensive search than it is to expand a search that was very limited in the first place. Once you have a general idea of the quality, and the "universe" (volume and distribution) of relevant information available on the toxicity of a chemical, the search can then be scaled down or expanded, as appropriate. Techniques for modifying your search strategy to produce the desired results will be discussed in the next chapter of this series.

Unfortunately, since many other chemicals will share part, or fragments, of the desired chemical's name, inexact matching can result in the retrieval of a large number of irrelevant results. For example, a search on the chemical "ethylene glycol" will retrieve references for ethylene glycol ethers (e.g. ethylene glycol monomethyl ether), as well all other chemicals that share this name fragment. The number of irrelevant search hits is further inflated by the retrieval of studies that may have investigated the effects of the particular chemical as part of a mixture, or formulated product, and/or may have been indexed on the chemical because it was used as a solvent or substrate. As a result, it is essential to carefully assess and verify the relevance of your search results to the chemical of interest. Furthermore, a multi-database search will lead to retrieval of duplicate references within and between databases, which necessitates the identification and removal of redundant records.

It should thus be kept in mind that the initial number of hits is not always reflective of the amount of literature available on a particular chemical. Conducting a preliminary search will help you decide whether it is necessary to further refine your search strategy. If a relatively small number of citations are retrieved upon an exhaustive preliminary search, it may actually be more efficient to quickly scan each of these in turn, rather than attempting to refine your search.

### Conclusion

While there is no exact recipe to follow, it is important to understand the literature search process, and to plan well. In constructing a search strategy for a specific chemical, the ultimate goal is to find the most relevant information available in the most efficient manner possible – without compromising the quality or exhaustiveness of the search.

*Chapter 3 in the CHEMINFO story discusses techniques and strategies to refine a search strategy. Cautious refinement of a search strategy can efficiently scale down a search that has retrieved a large number of hits or expand a search that has retrieved few or no hits.*

## Chapter Three: Searching Bibliographic Databases – A Refined Search

The identification of all relevant toxicity data is essential to making an accurate assessment of the potential health hazards of a chemical. In most cases, searching selected bibliographic databases is the most effective means to pinpoint original published literature. The "gold standard" is a search strategy that retrieves most or all of the pertinent citations, and the fewest irrelevant ones. This article reviews how to achieve the fine balance between limiting a search too much (excluding important information), and not limiting it enough (and retrieving a large, unmanageable number of hits).

### Techniques for Refining a Literature Search

Explicit guidelines must be developed to identify the types of documents that will and will not be useful for getting the answers required. The value of a particular document will depend on factors such as the:

- specific question/issue being addressed (e.g. are you conducting a comprehensive evaluation of the health effects of a chemical, or focusing on a specific effect such as carcinogenicity?);
- quantity, quality and originality of the information already available;
- time and costs potentially involved in obtaining the information.

Once the type of information you need has been defined, your search strategy can be targeted and refined using specific criteria.

#### *A. Non-Subject Specific Criteria*

The most straightforward technique for reducing the number of search results may be to restrict your search by non-subject specific parameters such as:

**Language of publication** – certain documents may only be available in a foreign language. In some instances, it may be necessary to have a document translated.

**Publication year** – focus on a particular date range (e.g. if you would only be interested in recent information, as opposed to historical).

**Publication/document type** – e.g. you may want to focus on high quality reviews

*Note:* Always apply caution when applying criteria to narrow your search.

#### *B. Subject Specific Criteria*

**Keywords**

You may want to restrict your search to a particular topic in order to retrieve a manageable amount of literature. For example, if you are only interested in studies that focus on a specific toxicological endpoint (e.g. mutagenicity), and not with everything that has been published on the health effects of the chemical, it is practical to construct a search strategy that will retrieve only this type of information.

To build a refined search strategy, identify the words or phrases that commonly appear in the titles or abstracts of the most relevant citations in your comprehensive search results. Using these keywords and phrases in your new refined search strategy will help maximize the retrieval of relevant citations.

For example, if you are looking for information on the mutagenic/genotoxic effects of acrylonitrile, your search strategy should combine the identification information for this chemical (synonyms, CAS Registry Number), with terminology that is specific to the field of genetic toxicology (e.g. "mutagen", "chromosome", "DNA").

**Subject Headings**

Many bibliographic databases index articles using a controlled vocabulary. One example is the National Library of Medicine's Medical Subject Headings (MeSH), which are included in MEDLINE, as well as some TOXLINE subfiles. By incorporating these targeted keywords in your search, all articles on the topic in question will be retrieved, regardless of the wording used by the author in the original article. Refer to the user guide to help develop an appropriate search strategy for the database you are consulting. For more information on the use of MeSH, refer to http://www.nlm.nih.gov/mesh/.

There are sometimes limitations in indexing, especially for historical information. Therefore, it is best to use a combination of approaches such as MeSH "subject headings", along with commonly used terms or keywords.

### Search Options and Operators

Searching for a particular keyword across all fields allows for maximum retrieval, but it also increases the number of irrelevant citations retrieved. Try restricting your keyword search to a particular field or index (e.g. abstract, title, keywords). For example, searching for "carbon monoxide" within the title field improves the chances of retrieving articles that focus specifically on this chemical, rather than on its use in other contexts (e.g. as a by-product).

In addition, using search operators such as "OR", "AND", or "NOT" can be combined with appropriate search terms to "zero in" on studies of interest. This technique is especially helpful when there is an abundance of information on a particular topic. For instance, specific toxicological endpoints for some chemicals may have been heavily studied, while there is little to no information on other endpoints. For example, quite a bit of information is available on the skin irritation properties of the detergent sodium lauryl sulfate, which are very well established relative to other endpoints. To more easily pinpoint other types of information, you may find it necessary to eliminate the studies that focused on skin irritation (through the use of "NOT") from your search results to reduce the volume of literature retrieved.

### Database/Subfile Selection

An important strategy for locating information is to understand which databases or subfiles are most likely to provide the highest yield of relevant items. Since major bibliographic databases such as MEDLINE serve the information needs of a wide spectrum of users, the chances of retrieving a large number of unwanted results are increased. Therefore, restricting your search to a smaller specialized database such as OSHLINE™ with NIOSHTIC®/NIOSHTIC-2, which focuses on occupational health and safety information, or a subject-oriented subfile such as the EMIC (Environmental Mutagen Information Centre) subfile of TOXLINE (genetic toxicity information) can produce the best and most relevant set of search results.

Referring back to the acrylonitrile mutagenicity example, optimum results are achieved by conducting an exhaustive search of the EMIC subfile of TOXLINE, a concentrated collection of genotoxicity information.

### Study Details/Methodology

Other inclusion/exclusion criteria can include: age groups (e.g. children versus adult), animal versus human studies, in vivo versus in vitro studies, or route of exposure (e.g. oral versus intravenous exposure). For example, for CHEMINFO, all studies that use non-occupationally relevant routes of exposure (e.g. intravenous) are excluded.

It should be emphasized that details such as the study methodology are not always included within the bibliographic information. The most reliable way to incorporate these exclusion criteria is to review the full text article. CHEMINFO staff always obtain and evaluate original information, rather than relying on abstracts or secondary sources. Techniques on how to evaluate toxicological and human health information will be reviewed in the next chapter in this series.

### Scope

Sometimes, regardless how refined or targeted your search, you may still have to sift through thousands of relevant results. In this situation, it is helpful to identify well-conducted, exhaustive review papers from which the best quality research evidence can be identified. For example, when there is an overwhelming volume of relevant literature on a well-researched chemical such as benzene, CHEMINFO staff will temporarily set aside the search results and use peer-reviewed review articles, like the Concise International Chemical Assessment Documents (CICADS) from the World Health Organization, to identify key papers. Original papers are always obtained and reviewed in detail to support conclusions and classification decisions, or to resolve or better understand controversial or complex issues.

Once it has been determined what information is available from the reviews, and key studies have been examined, you can conduct highly targeted supplementary searches to identify new information, or information that is missing or has not been adequately evaluated.

In conclusion, keep in mind that a search technique that works for one chemical, may not apply to another. In all cases, it is necessary to carefully appraise the overall picture presented by your preliminary search results. From there, a refined search strategy can be developed that is unique to the chemical of interest, and the issues presented by the available research. Whatever strategy you implement, carefully document the techniques that were used to identify and select information, so that the search can be reused in the future, as appropriate.

*Chapter 4 in the CHEMINFO story discusses how to apply an evidence-based approach to evaluating animal toxicity studies when assessing the potential occupational health hazards of a chemical.*

## Chapter Four: Evaluation of Animal Toxicity Information

There are many different types of animal toxicity tests, which help us understand how chemicals can affect people exposed to them at work. In fact, many regulatory systems that assess and classify potential hazards to humans are largely based on the use of animal toxicity information e.g. LD50's, skin and eye irritation tests, and carcinogenicity studies.

Several factors must be considered when reviewing animal toxicity studies and assessing their relevance to the chemical in question and to occupational health and safety. These factors include proper identification of the test substance, appropriateness of the route of exposure, the dose levels used, the choice of test animals or species, the use of a control group, the number of test animals/group, and the duration of the exposure and observation period.

### Identification of the Test Substance

Proper identification of the test substance is important so that you know the results of the study are relevant to the specific chemical or mixture that you are interested in. This task may appear to be a simple matter of matching names, but this is not always the case.

For example, the non-specific, chemical name "propylene glycol monomethyl ether" loosely refers to two different forms (isomers) of this chemical - the alpha and beta isomers. The alpha isomer (1-methoxy-2-propanol; CAS No. 107-98-2) is not teratogenic in animal studies, while the beta isomer (2-methoxy-1-propanol; CAS No. 1589-47-5) is teratogenic. The commercial product largely consists of the alpha isomer. Searching on the non-specific name of "propylene glycol monomethyl ether" will find literature that relates to either one or both of the isomeric forms. Therefore, care must be taken in sorting out which isomer was studied by examining synonyms used by the author, the CAS Registry Number (a unique identifier) and physical properties.

The presence of an impurity or additive can also significantly alter the results of a toxicological test. For example, inhibitors are added to unstable chemicals. In the case of acrylamide, copper salts are used as inhibitors. Some copper salts are known to cause skin sensitization. Positive results from a skin sensitization test conducted with inhibited acrylamide do not provide conclusive evidence that acrylamide is a skin sensitizer unless the use of copper salts can be ruled out.

### Route of Exposure

Toxicological studies are conducted for many different purposes and, thus, use many different routes of exposure, e.g. ingestion, inhalation, intraperitoneal, intravenous, and intracranial.

It is relevant for pharmaceutical companies to evaluate the hazards of medications that are injected directly into the blood stream (intravenously) or into the abdomen (intraperitoneally). Therefore, databases like TOXLINE and RTECS® contain studies that used these and many other routes of exposure to administer a chemical. However, for the purposes of evaluating occupational health hazards, only four routes of exposure have direct relevance – inhalation, skin contact, eye contact and ingestion. Other types of studies can shed light on mechanisms of toxicity, but are not as relevant for assessing the occupational hazards.

Even if the chemical is inhaled, ingested or comes into contact with the skin or eyes, one must consider if the method of exposure is relevant to the chemical being studied. For example, sometimes, extreme measures are taken to get animals to inhale chemicals that are not normally very easily inhaled. While one would not normally expect to "ingest" a gas, some studies have been conducted with super-cooled gases, which would be in a liquid state. Non-volatile solids and liquids have been ground up, burned up, and heated to boiling to produce an airborne concentration that can be inhaled. These studies can be relevant if the exposure method is relevant to how the chemical is processed or used in the workplace (i.e. the process involves grinding or heating to a molten state). Studies where the chemical is burned and animals are exposed to the combustion and thermal decomposition products are relevant to firefighter exposures. However, these studies must be carefully evaluated within the context of assessing the hazards of the chemical during typical processing and handling in the workplace.

### Dose Levels

Ideally, a well-conducted toxicological study will use at least three dose levels. A high dose where there are definite signs of toxicity; a middle dose that produces minimal signs of toxicity; and a low dose that produces no signs of toxicity. Range-finding studies are sometimes used to help determine the appropriate dose levels.

The use of three doses assists in determining a dose-response curve, which shows the pattern of toxicity of a chemical. If only one dose is used, the experiment will not provide enough information on the toxicity at higher or lower doses. In general, toxicity increases with dose. If a certain observation does not follow a dose-response curve, it is possible that the observation was due to chance, rather than a true effect. If only one dose is administered, the study observations may be of limited usefulness.

However, sometimes researchers will have thoroughly evaluated earlier studies and select a highly targeted dose. This type of study is a highly refined study designed to show if a chemical is capable of causing a specific effect at a specific dose. The use of this technique allows the researcher to establish a cause-effect relationship, while reducing the number of laboratory animals. Thus, the use of a single dose does not necessarily invalidate the observations of a study if they are interpreted within the context of the earlier studies.

### Species

Certain animal species are used extensively for certain types of toxicological tests. For example, rabbits are used extensively to study skin and eye irritation effects. As a result, there is an extremely large body of comparative data available to assess the skin and eye effects in rabbits. Results with other species are not necessarily excluded from the assessment of skin and eye irritation, but comparison and evaluation is more difficult.

Some animal species are very susceptible to certain effects of chemicals. For example, cats are very sensitive to developing methemoglobinemia, a blood effect. It may be justifiable to use cats if the researchers are trying to determine if a specific chemical will cause methemoglobinemia under any circumstances. However, in general, a positive methemoglobinemia response in cats must be interpreted with caution.

### Environmental Conditions

Environmental factors can also influence the outcome of an experiment, for example:

**temperature** – high or low temperatures could affect fertility test results;

**humidity** – could influence the amount or particle size of the chemical in the air;

**caging** – crowding could cause stress-related illness;

**diet/water** – dietary deficiencies (e.g. zinc deficiency) could cause harmful effects, as could the presence of impurities in food or water;

**acclimatization** – a change in environmental conditions could affect breeding behaviour.

### Control Group

A control group provides a standard of comparison for the experimental groups. Characteristics of the control group such as species, age and sex should match the experimental groups. The control group is handled in exactly the same way as the experimental groups, except there is no chemical exposure. Results obtained for the experimental groups are compared to each other (the 3 dose groups) and to the control group to determine if statistically significant changes occurred.

An animal can be used as its own control, but only for skin/eye irritation studies, because the experiment is looking for a local effect at the site of application. For example, one eye can be used to test for irritation and the other eye serves a control.

A vehicle control is used if the chemical is not a liquid or water-soluble and must be dissolved in a vehicle or carrier so that it can be easily administered to the animals. A vehicle control is necessary so that it can be demonstrated that exposure to the vehicle did not cause any harmful effects.

### Number of Test Animals

The appropriate number of test animals varies depending on the study type. Generally, the longer the study and the more subtle the effect that is being evaluated, the more animals required per dose group. Acute lethality studies generally need 5 animals per dose group, while a carcinogenicity study needs 100 animals per dose group. The more animals per group the higher the statistical power of the study and the more likely that a rare or subtle effect will be observed.

### Duration of Exposure/Observation Period

The duration of exposure depends on the type of test and, sometimes, on the route of exposure used in the test The post-exposure observation period must be sufficiently long to determine the full extent of the effects of exposure and to determine if the observed effects are reversible.

Oral acute lethality (LD50) exposures involve a single exposure to the test chemical, while inhalation acute lethality (LC50) testing involves exposure for 4 hours. Carcinogenicity tests are generally conducted for the entire lifespan of the animal (18 months for mice and hamsters; 24 months for rats). If the exposure duration is too short, there will not be enough time for effects with a long latency period, like cancer, to develop.

For acute lethality testing, animals are observed for 14 days following exposure. Inhalation of a severe lung irritant can result in delayed deaths, since it takes time for the full injury of the lungs to develop. If the observation period is only 7 days, the inhalation hazard of the chemical may be reported inappropriately low.

## Guidelines

How does one know how many animals are enough animals? Which is the preferred species? What duration of exposure is appropriate for a specific type of test?

Fortunately, the answers to these questions are provided by a group of international experts under the umbrella of the Organization for Economic Cooperation and Development (OECD). The result is a series of internationally accepted guidelines for the conduct and evaluation of toxicological tests called the "OECD Guidelines for Testing of Chemicals – Health Effects". For information on OECD, including a complete list of guidelines, see www.oecd.org.

A word of a caution - if the study design does not exactly match the OECD guidelines, the results are not necessarily invalid. Overall, it is important to consider the quality of the study design and reporting, as well as other factors such as the behaviour of closely related chemicals and an evaluation of all of the literature available on the substance when assessing the overall reliability and relevance of the observations. For example, if the OECD guidelines are followed to the letter, the results of an otherwise well conducted experiment that used 17-18 animals/group in a developmental toxicity study (instead of the recommended 20) could wrongly be dismissed or minimized. However, a developmental toxicity study that used a single dose (rather than 3 doses) in a study with only 8 animals/group should not be used to conclude that a chemical is or is not a developmental toxin.

## Conclusion

There are many advantages to using animal toxicity studies to assess workplace hazards.

In a well-designed study:

- there is a comparative control group,
- enough animals are used so that subtle responses can be measured and statistically evaluated,
- long-term exposure to a single chemical or a well-defined mixture is possible,
- there is a large body of comparative data, and
- animal tests can be highly predictive of effects on humans.

There are, however, disadvantages to animal toxicity testing. No matter how well conducted a study is, it is always necessary to extrapolate the findings to humans. Sometimes, effects are observed that are "species-specific". For example, some chemicals cause an effect only in the male rat kidneys (hyaline droplet nephropathy). This effect will not be observed in humans, and is not even observed in female rats. Animal experiments commonly use high exposure levels, which may never be encountered in a work environment. The exposure scenarios are never "real-life", because humans are never exposed to a single chemical for 6 hours/day, 5 days/week and there are a variety of lifestyle factors that come into play, e.g. diet, exercise, smoking, alcohol consumption.

*Next in our series, we consider the challenges of reviewing and drawing conclusions from human case reports and epidemiological studies.*

**For more information about our CHEMINFO database, or any of the products listed, please visit www.ccohs.ca or contact Client Services at 1-800-668-4284 or clientservices@ccohs.ca.**

### Table 1: SOURCES OF OCCUPATIONAL TOXICOLOGY INFORMATION USED FOR CHEMINFO

#### CHEMICAL DIRECTORY DATABASES

FREE **CHEMINDEX**
Canadian Centre for Occupational Health and Safety (CCOHS) (http://ccohs.ca)
URL: http://www.ccohs.ca/products/databases/ chemindex.html

FREE **ChemIDplus**
U.S. National Library of Medicine (NLM) (http://www.nlm.nih.gov/)
URL: http://chem.sis.nlm.nih.gov/chemidplus/

#### BIBLIOGRAPHIC DATABASES

**OSHLINE™ with NIOSHTIC®/NIOSHTIC-2**
Canadian Centre for Occupational Health and Safety (CCOHS) (http://ccohs.ca)
URL: http://www.ccohs.ca/products/web/nioshtic.html

**TOXLINE® on CCINFOdisc**
U.S. National Library of Medicine (NLM)
Available from: Canadian Centre for Occupational Health and Safety (CCOHS) (http://wwwccohs.ca)
URL: http://www.ccohs.ca/products/databases/ toxline.html

#### DIRECT INFORMATION / FULL TEXT DATABASES

**Hazardous Substances Databank (HSDB®)**
U.S. National Library of Medicine (NLM)
Available from: Canadian Centre for Occupational Health and Safety (CCOHS) (http://ccohs.ca)
URL: http://ccohs.ca/products/databases/hsdb.html

**Integrated Risk Information System (IRIS)**
U.S. Environmental Protection Agency (EPA) (http://www.epa.gov/)
URL: http://www.epa.gov/iris/

**Registry of Toxic Effects of Chemical Substances (RTECS®)**
National Institute for Occupational Safety and Health (NIOSH)
Available from: Canadian Centre for Occupational Health and Safety (CCOHS) (http://ccohs.ca)
URL: http://www.ccohs.ca/products/databases/ rtecs.htm

#### DIRECT INFORMATION / FULL TEXT PUBLICATIONS

FREE **ATSDR Toxicological Profiles**
Agency for Toxic Substances and Disease Registry (ATSDR): Public Health Service, U.S. Department of Health and Human Services (http://www.atsdr.cdc.gov)
URL: http://www.atsdr.cdc.gov/toxpro2.html

FREE **Concise International Chemical Assessment Documents (CICADs)**
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The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and The Dutch Expert Committee on Occupational Standards.
National Institute for Working Life (http://www.niwl.se/)
URL: http://www2.niwl.se/forlag/en/ah.asp

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