

Final Report

**Biomarkers of Environmental Health and Safety Risks to Children for
Use in a Longitudinal Cohort Study – Update**

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1. Introduction

The following report describes a project that continued to develop and populate a bibliographic database in support of the National Children’s Study. The purpose of this work assignment was to identify recently published literature that may be relevant to biomarkers and children’s health and to add the literature citations to the existing database. Another purpose was to make enhancements to the search capabilities of the database and to update the User’s Guide (**Attachment 1**). The database contains literature on biomarkers of exposure, susceptibility, or effect, and an associated health outcome. Literature identified during the search was captured in an electronic database and reviewed for relevance. The final database, called the Biomarkers Database, is a searchable reference tool that scientific investigators may use for future research efforts.

The work assignment included a literature search, abstract screening process, revision of a pre-existing database, search enhancements to the database, and revision of a User’s Guide. We reviewed the search strategy and revised several of the search terms using the terms provided in the Final Report and User’s Guide from August 25, 2003. We protected the integrity of the pre-existing data in the Biomarkers Database and only added new records. Previously, the Biomarkers Database contained 4,336 records; after our literature search, the database contains 5,889 records. In addition, new search features were added to the database, providing the ability to search on multiple terms in the majority of the fields. The User’s Guide was also added into the database.

2. Literature Search

We began the task of updating the Biomarkers Database by reviewing the PubMed ([www.ncbi.nlm.nih.gov/entrez.query.fcgi](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi)) MESH (Medical Subject Headings) search terms to ensure their currency and ensure that syntax was correct. Since some of the terms were more general, several new MESH headings were suggested for several of the search strings. After conferral with the EPA Work Assignment Manager (WAM), several of the search strings were revised and some of the Boolean logic—including placement of the parentheses—was tightened up. **Table 1** shows the original search terms and changes made. Each search return was displayed in “MEDLINE” format, downloaded to Reference Manager version 10 (RefMan), and finally converted to comma-delimited format and saved as a *.txt file. The text file was converted to Excel format. The Excel file was then converted into Access format, and the Access programmer added all the citations into the database using the “Append” command.

The date limits searched were from July 1, 2003 to the day of the search, June 23, 2004. **Appendix A** shows the search criteria and limitations as performed on June 23, 2004. A total of 1,153 articles were identified in the initial search and added to the Biomarkers Database.

Table 1
PubMed Search String Details and Changes Made in June 2004

Search Terms and PubMed Search Details	Limitations	Approved search strategy changes (if any)
(biomarker* or biological Markers [MESH]) AND exposure AND environmental pollution ("biological markers" [Mh] OR biomarker [TW]) AND exposure[ALL])	7/03-Present; English, Review	None
molecular epidemiology ("epidemiology, molecular"[Mh] OR molecular epidemiology[TW])	7/03-Present; English, Review	None
biomonitor* AND expos* (biomonitor[ALL] OR biomonitored[ALL]) OR biomonitoring[ALL]) OR biomonitors[ALL]) OR biomonitoring[ALL]) AND (expos[ALL])	7/03-Present; English, Review	Add Environmental monitoring[mh] using "OR" with biomonitor*
genetic marker* AND (biomarker* OR "biological markers"[MAJR]) (genetic marker[ALL] OR genetic markers[ALL]) OR genetic markers/analysis[ALL]) OR genetic markers/blood[ALL]) OR genetic markers/genetics[ALL]) OR genetic markers/immunology[ALL]) OR genetic markers/physiology[ALL]) OR genetic markers/urine[ALL]) AND ((biomarker[ALL] OR biomarker/polymerase[ALL]) OR biomarkers[ALL])) OR "biological markers"[MAJR])	7/03-Present; English, Review	None
predisposition to disease AND biomarker ("disease susceptibility"[Mh] OR predisposition[TW]) AND ("disease"[Mh] OR disease[TW])) AND ((biomarker[ALL] OR biomarker/polymerase[ALL]) OR biomarkers[ALL])) OR "biological markers"[MAJR])	7/03-Present; English, Review	None
metabolit* AND expos* (metabolit* [ALL]) AND (expos*[ALL])	7/03-Present; English, Review	None
fetus AND biomarker ("fetus"[Mh] OR fetus[TW]) AND ("biological markers"[Mh] OR biological marker[TW])	7/03-Present; English, Review	None
pregnancy complications AND biomarker ("pregnancy complications"[Mh] OR pregnancy complications[TW]) AND ("biological markers"[Mh] OR biomarker[TW])	7/03-Present; English, Review	None
pregnancy outcome AND biomarker ("pregnancy outcome"[Mh] OR pregnancy outcomes[TW]) AND ("biological markers"[Mh] OR biomarker[TW])	7/03-Present; English, Review	None

Search Terms and PubMed Search Details	Limitations	Approved search strategy changes (if any)
<p>(pesticides[MESH] OR pesticide*) AND ("biological Markers"[MESH] OR biomarker*) ("pesticides"[Mh] OR (pesticide[ALL] OR pesticide/animal[ALL]) OR pesticide/herbicide[ALL]) OR pesticide/m2[ALL]) OR pesticide/solvent[ALL]) OR pesticideformulating[ALL]) OR pesticides[ALL]) OR pesticides/analysis[ALL]) OR pesticides/blood[ALL]) OR pesticides/chemistry[ALL]) OR pesticides/classification[ALL]) OR pesticides/commodities[ALL]) OR pesticides/economics[ALL]) OR pesticides/fertilisers[ALL]) OR pesticides/fertilizer[ALL]) OR pesticides/history[ALL]) OR pesticides/immunology[ALL]) OR pesticides/metabolism[ALL]) OR pesticides/metabolites[ALL]) OR pesticides/pharmacokinetics[ALL]) OR pesticides/pharmacology[ALL]) OR pesticides/poisoning[ALL]) OR pesticides/standards[ALL]) OR pesticides/toxicity[ALL]) OR pesticides/urine[ALL]) OR pesticides/weedicides[ALL])) AND "biological Markers"[MH]) OR (biomarker[ALL] OR biomarker/polymerase[ALL]) OR biomarkers*[ALL])</p>	7/03-Present; English	None
<p>effect biomarker AND exposure (effect[ALL] AND ("biological markers" [Mh] OR biomarker[TW]) AND exposure[ALL])</p>	7/03-Present; English, Review	Add an "AND" in between effect and biomarker
<p>susceptibility biomarker AND exposure ("disease susceptibility"[Mh] OR Susceptibility[TW]) AND ("biological markers"[Mh] OR biomarker [TW]) AND exposure[ALL])</p>	7/03-Present; English, Review	Add an "AND" in between susceptibility and biomarker
<p>("air pollution"[MESH] OR "air pollutants" [MESH] OR air pollut*) AND ("biological markers" [MESH] Or biomarkers*) ("air pollution"[MH] OR "air pollutants"[MH]) OR (air pollutant[ALL] OR air pollutants[ALL]) OR air pollutants/analysis[ALL]) OR air pollutants/blood[ALL]) OR air pollutants/chemistry[ALL]) OR air pollutants/classification[ALL]) OR air pollutants/economics[ALL]) OR air pollutants/history[ALL]) OR air pollutants/immunology[ALL]) OR air pollutants/metabolism[ALL]) OR air pollutants/pharmacokinetics[ALL]) OR air pollutants/pharmacology[ALL]) OR air pollutants/poisoning[ALL]) OR air pollutants/standards[ALL]) OR air pollutants/toxicity[ALL]) OR air pollutants/urine[ALL]) OR air polluted[ALL]) OR air polluting[ALL]) OR air pollution[ALL]) AND "biological markers"[ALL])</p>	7/03-Present; English	None
<p>asthma AND biomarker ("asthma"[Mh] OR asthma[TW]) AND ("biological markers"[Mh] OR biomarker[TW])</p>	7/03-Present; English,	None
<p>respiratory health AND biomarker (respiratory[ALL] AND ("health"[Mh] OR health[TW]) AND ("biological markers"[Mh] OR biomarker [TW])</p>	7/03-Present; English,	None
<p>asthma AND biomarker AND exposure asthma AND exposure[ALL] AND biomarker* OR biological Markers [MH]</p>	7/03-Present; English,	None

Search Terms and PubMed Search Details	Limitations	Approved search strategy changes (if any)
("respiratory tract diseases" [MAJR] OR asthma) AND ("biological Markers" [MESH] OR biomarker*) ("respiratory tract diseases"[MAJR] OR ("asthma"[Mh] OR asthma[TW])) AND "biological Markers"[MH] OR ((biomarker[ALL] OR biomarker/polymerase[ALL]) OR biomarkers[ALL])	7/03-Present; English,	None
cancer AND biomarker ("neoplasms"[Mh] OR cancer [TW]) AND ("biological markers"[Mh] OR biomarker[TW])	7/03-Present; English, Review	None
cancer AND biomarker AND pregnancy (biomarker* OR biological markers) AND (cancer OR neoplasms) AND pregnancy	7/03-Present; English, Review	None
cancer AND biomarker AND pregnancy AND exposure (biomarker* OR biological markers) AND (cancer OR neoplasms) AND pregnancy	7/03-Present; English, Review	None
autism AND biomarker ("autistic disorder"[Mh] OR autism[TW]) AND ("biological markers [Mh] OR biomarker[TW])	7/30-Present; English,	None
neurodevelopmental disorders AND exposure (neuro[ALL] AND ("developmental disabilities"[Mh] OR developmental disorders[TW]) AND exposure[ALL])	7/03-Present; English,	None
developmental disability AND biomarker ("developmental disabilities"[Mh] OR Developmental disabilities[TW]) AND ("biological markers"[Mh] OR biomarker[TW])	7/03-Present; English,	None
(neurotoxicity OR neurotoxicology) AND biomarker (("neurotoxicity syndromes"[Mh] OR neurotoxicity[TW]) OR neurotoxicology[ALL]) AND ("biological markers"[Mh] OR biomarker[TW])	7/03-Present; English, Review	None
neurological development AND biomarker (neurological[ALL] AND (("growth and development"[mh] OR "human development"[Mh]) OR development[TW])) AND ("biological markers"[Mh] OR biomarker[TW])	7/03-Present English, Review	Add in "OR" Nervous system/growth and development with neurological development
injury and biomarker ("wounds and injuries"[Mh] OR injury [TW]) AND ("biological markers" [Mh] OR biomarker [TW])	7/03-Present; English, Review, Child 0-18	Eliminate Child limit
injur* AND exposure AND adverse effects (Wounds and Injuries [MH] OR injur*[ALL]) AND exposure[ALL]) AND ("adverse effects"[Mh] OR adverse effects[TW])	7/03-Present; English, Review, Child 0-18	Eliminate Child limit
biological marker [MESH] coordination AND exposure ("biological markers"[Mh] AND ("organization and administration"[Mh] OR coordination[TW])) AND exposure[ALL])	7/03-Present English, Review	None
(biological marker [MESH] or biomarker*) AND impulsive behavior ("biological markers"[Mh] OR ((biomarker[ALL] OR biomarker/polymerase[ALL]) OR biomarkers[ALL])) AND ("impulsive behavior"[Mh] OR impulsive behavior[TW])	7/03-Present English, Review	Remove * after biomarker (not consistent with other searches)

Search Terms and PubMed Search Details	Limitations	Approved search strategy changes (if any)
HOXA gene	7/03-Present; English, Review	“OR” Homeodomain proteins[mh] “OR” Hoxa protein[mh]
GABA	7/03-Present; English, Review	“AND” it with (biomarker OR marker)
Ubiquitin	7/03-Present; English, Review	None
VIP	7/03-Present; English, Review	“OR” Vasoactive Intestinal Peptide[mh]
Purkinje cells	7/03-Present, English, Review	None
meconium	7/03-Present, English, Review	None
saliva	7/03-Present, English, Review	“AND” it with (biomarker “OR” marker)

3. Elimination of Duplicate Citations

Citations from the set of text files were sorted and managed using Reference Manager Version 10.0 (RefMan®), a proprietary product of ISI ResearchSoft. An original database was created in RefMan® and the *.txt files were imported using the “Import Text File” function under a PubMed.cap filter. Preferences were set such that duplicate citations were not imported. RefMan® supplied each reference with a nonduplicate, nonsequential reference identification number upon import. These numbers were used during citation review to eliminate duplication of effort among the review team members.

4. Changes to the User’s Guide

The User’s Guide was updated to reflect the enhanced search capabilities of the database, and provide specific instructions on how to use the new capabilities. Most of the screen shots were replaced to show the new screens with the new features. Instructions are provided on how to use the new “AND” and “OR” searching capabilities.

The User’s Guide also shows the updated search terminology used and reflects the date of the PubMed search. The revised User’s Guide is included as **Attachment 1** and is included on the CD-ROMs with the updated editable and un-editable versions of the Biomarkers Database.

5. Title and Abstract Review Process

Each abstract was reviewed and given a Pass, Fail, or Cannot Ascertain rating to identify those with relevant biomarker information. Using criteria from the User’s Guide and previous final report, the review team developed a standard document to rate the abstracts. The document also reduced the inter-rater variability among the review team. One minor change was made in July 2004 to the review criteria. Instead of research conducted on “humans, mammals, or birds,” the criteria became “animals.” The revised “Pass/Fail Criteria for Abstract Review” is included as **Attachment 2** to this report.

Abstracts were divided evenly among the team, and the team frequently communicated to clarify and expand upon standards of review. The team read each title and abstract (when abstract was included) and assigned each a determination of pass/fail/cannot ascertain. A total of 221 abstracts, 19% of the 1,153 identified during the search, passed the biomarker review criteria. This is the same percentage of passed citations as last year's update. **Section 8** includes information on observations we made regarding the high number of fails and some possible solutions to remove irrelevant or ineligible citations during the search stage. After reviewing the abstracts in MS Access, the three reviewers uploaded their version of the database into an ftp site. The Access programmer then merged all three versions into one master database, which incorporated the reviews.

Biomarker information was completed for each passed abstract in the MS Access database. The review form collected information such as biomarker name, type, health outcome category, specific health outcome, and specimen type. Each passed abstract yielded one or more biomarker names and the associated health outcome.

Failed abstracts were given a "reason for failure" that included "no health outcome," "prognosis only," "treatment only," "medical test," "clinical trial," "research methods," "biomarker measured in tumor only," "other," and "irrelevant." The "irrelevant" category included abstracts discussing the elucidation of a biological pathway or signal cascade with no mention of a specific biomarker or adverse effect. The "other" category included citations with no adverse effect and, when obvious from the title, all of the preceding categories. A significant number of citations (n=126) did not have an abstract to review, most of which were subsequently assigned as "cannot ascertain." However, this is a slightly lower percentage than last year's update (10% versus 13%). The same process used to merge the review information was applied to merge the biomarker information from the three reviewers into the Access database.

6. Quality Control

After the abstracts were screened, a 10% sample underwent a quality control (QC) review. The QC staff employed the same scoring standards as the review team, with the exception of the revised "animal" criteria. Upon completion of the QC review, the RTI Work Assignment Leader (WAL) compared the results. The QC yielded an 89% agreement rate for passed and failed abstracts. Two of the reviewers had a 5% and 7% disagreement rate respectively, which was acceptable under the agreed-upon quality review criteria. However, there was a 25% disagreement rate with a third reviewer, so an additional 100 citations from that reviewer were quality checked. The discrepancy was related in part to inter-rater variability and, to some extent, to the amount of information offered by reviewing just the title, keywords, and abstract. Also, there were a number of citations that passed under the new "animal" criteria, but not under the "humans, mammals, or birds" criteria. The WAL reviewed all discrepancies in the QC sample and updated the records appropriately. By request of the WAM, the WAL added in a variable to indicate the reviewer organization (subcontractor or RTI) to the reviewer initial field. The WAL reviewed all of the added citations at the same time, which provided an additional QC on all of the citations.

7. Searching and Other Capability Enhancements Added to the Biomarkers Database

The Access programmer added search enhancements to the database, enabling a searcher to search on multiple terms within the same field. For example, more than one biomarker or year can now be searched at one time using the "OR" capability. The fields enhanced in the Search Biomarkers section include Biomarker Name, Health Outcome Category, Health Outcome Description, Biomarker Type, Exposure, and Specimen Type. The fields enhanced in the "Search Citations" section were Author, Year, and Keyword. For fields that have pull-down selections, more than one term can be selected at a time using the "Ctrl" key. For fields that require keying, terms need to be put on separate lines. The WAL tested the search enhancements during the whole process and offered suggestions for improvements,

which were implemented. In addition, the WAL requested that the Project Director also test the database to make sure that a novice user would not have any problems using the different fields.

After review of the “Draft” database by the WAM, a request was made to also add an “AND” search capability to the Keyword field in the “Search Citations” section. The Access programmer added that feature to the Keywords field, and also to the other fields that have to be searched using typed-in terms. In total, the Keyword, Author, Health Outcome Description, and Exposure fields all have the capability to search multiple terms using the “AND” or “OR” options. A pull-down menu option was added to provide this capability. “Match Any Phrase” is the “OR” option and “Match All Phrases” is the “AND” option. A further description of and instructions for searching in those fields are provided in the appended **User’s Guide (Attachment 1)**.

One last feature was added to the database, as suggested by the Project Director and approved by the WAM. The User’s Guide was converted to .pdf format, and the file (help.pdf) was linked within the Biomarker Database for easy referral. A button was added to the opening page of the database enabling users to display the guide with one click.

8. Problems and Solutions

The need to review and update the search terms, while preserving the intent of the Biomarkers Database, was time consuming. However, it was necessary to provide the best database update possible, and will have to be done for every update.

A high fail rate (81%) for the citations retrieved by the PubMed database is due to the nature of the subject matter. In order to retrieve the highest number of relevant citations, some precision was lost. There is no perfect method to eliminate citations that discuss treatment, therapy, or prognosis. However, some citations could be eliminated from the initial search with a few revisions to the search criteria or search terms used. There were also a high number of citations that did not pass because they discussed tumor markers exclusively. Upon careful review of the MESH headings assigned by NLM indexers, no citations in the Biomarkers Database had both of the MESH terms Biological Markers and Tumor Markers in the keywords section, only one or the other. Therefore, it may be possible to “Not out” the tumor marker citations by using the “NOT” command in the Cancer search string.

**USER'S GUIDE
Biomarkers Database**

Revised August 25, 2004

I. INTRODUCTION

As part of the U.S. Environmental Protection Agency's (EPA's) Biomarkers of Environmental Health and Safety Risks to Children for Use in a Longitudinal Cohort Study Task, a literature search was conducted. The references obtained from the literature search were stored electronically in a Microsoft Access 2000 database. Reviews of the references and abstracts were also stored in the database. In addition to a summary report on the literature search, this database (referred to as the Biomarkers Database) was delivered to EPA on August 25, 2004.

The literature search focused primarily on peer-reviewed literature, using PubMed as the main source of information. References were obtained for articles that met the search criteria summarized in Table 1 (the full search strings are listed in **Appendix A**). The literature search for relevant *review* and *primary* articles was conducted on June 23, 2004. This current search was an update from a search conducted on July 17, 2003 (review articles) and July 25, 2003 (primary articles) and included all articles published from July 1, 2003 to the date of the search (June 23, 2004). See **Table 1** for a summary of the search terms used and the limitations used in this update.

Each reference and its abstract and keywords were reviewed and screened in terms of relevancy to EPA's goals. To pass the initial review, the title and/or abstract must have met the following criteria:

1. Consisted of a review article, or a recent primary study, or a primary study on an emerging topic that is not elsewhere reviewed in the literature.
2. Contained (or at least presented an adequate impression that the full article may provide) the following data in animals (any life stage):
 - at least one biomarker of exposure, susceptibility, or effect (terms defined in **Appendix B**); and
 - an adverse health outcome (while the focus was on cancer, respiratory health/asthma, developmental disability/autism, unintentional injury, and other health outcomes were included as well).

Note: An exposure did not have to be discussed in the title/abstract to pass the screen. All exposures were considered relevant, with the exception of medical treatments. Keywords were also used as a criteria for pass/fail.

3. Published in the time period designated for the health outcome category, as described above.

References that did not meet these criteria were marked as Cannot Ascertain or Fail. The Cannot Ascertain result code meant that the title and/or abstract were not detailed enough to determine whether the criteria were met or not. The Fail result code meant that the abstract did not meet the criteria. For some of the references marked as Cannot Ascertain, a further review was conducted on the article to determine if the criteria were met and a new result code was given.

Table 1. Summary of Keyword Search Strings and Search Limitations

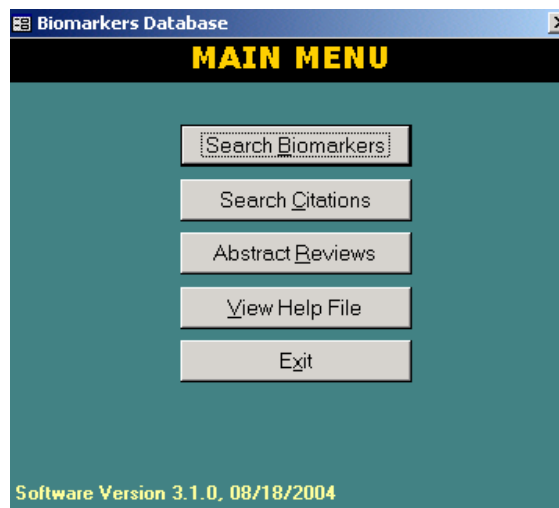
Category	Keyword Search Strings	Limitations
General	1. biomarker AND exposure AND environmental pollution. 2. molecular epidemiology 3. (biomonitor or environmental monitoring) AND exposure 4. genetic marker AND biomarker 5. predisposition to disease AND biomarker 6. metabolite AND exposure 7. fetus AND biomarker 8. pregnancy complication AND biomarker	7/1/03-6/24/04, English, Review “ “ “ “ “
Exposure	9. pesticides AND biomarker 10. air pollution AND biomarker 11. effect biomarker AND exposure 12. susceptibility biomarker AND exposure	7/1/03-6/24/04, English, Review “ “
Asthma	13. asthma AND biomarker 14. respiratory health AND biomarker 15. asthma AND biomarker AND exposure 16. respiratory tract diseases AND biomarker	7/1/03-6/24/04, English “ “ “
Cancer	17. cancer AND biomarker 18. cancer AND biomarker AND pregnancy 19. cancer AND biomarker AND pregnancy AND exposure	7/1/03-6/24/04, English, Review “ “
Neurodevelopmental Disorders	20. autism AND biomarker 21. neurodevelopmental disorder AND exposure 22. developmental disability AND biomarker 23. neurotoxic* AND biomarker 24. neurological development AND biomarker	7/1/03-6/24/04, English, “ “ “ “ “
Injury	25. injury AND biomarker 26. injury AND exposure AND adverse effects 27. coordination AND biomarker AND exposure 28. impulsive behavior AND biomarker AND exposure	7/1/03-6/24/04, English, Review “ “ “
Miscellaneous	29. HOXA gene OR homeodomain proteins OR hoxa proteins 30. GABA AND (biomarker OR marker) 31. Ubiquitin 32. VIP OR vasoactive intestinal peptide 33. Purkinje cells 34. Meconium 35. Saliva AND (biomarker OR marker)	7/1/03-6/24/04, English, Review “ “ “ “ “ “

The Biomarkers Database contains all references obtained during the literature search, including those abstracts marked as Cannot Ascertain or Fail. It has 5,889 citations (most with abstracts), and some basic information extracted from each abstract text. The default setting for the search procedures described below is the set of references that met the criteria above and passed the screen.

II. BIOMARKERS DATABASE

The Biomarkers Database was designed to serve three purposes: (1) to allow users to search the biomarker records compiled, (2) to allow users to search the citations file, and (3) to allow users to read the abstract reviews. Only references that passed the screening criteria are accessed during the default search procedure. This default can be changed on the Biomarkers Search and the Citations Search screens. The Abstract Reviews screen lists all references in the database.

Figure 1. Database Main Menu



Two versions of the Biomarkers Database were provided to EPA. One version allows the user to view the contents of the database without making any modifications or additions. The other "editable" version allows users to modify the database's contents and to add additional references. Both versions of the database require the user's computer to have Microsoft Access installed. Since the databases were developed in Microsoft Access 2000, this is the preferred version of Access to use. However, newer versions of Access should be functional. If Access 2000 is not being used, a message may appear about converting the database to the newer version of Access upon opening the database. It is recommended that users do NOT convert the database.

A. SEARCHING BIOMARKER INFORMATION

Most of the biomarker information recorded in the database was obtained from abstracts, but some information is found in the Keywords too. During the abstract review process, each reviewer added the name of any biomarker(s) that were discussed in the references abstract. In addition, if available, the biomarker type, health outcome, specimen type, and exposure were recorded.

The Biomarker Search procedure allows the user to search the Biomarkers table in the database by defining a search term or terms for one or more fields. In the Main Menu screen, the user clicks the Search Biomarkers button to open the Search Biomarkers screen (**Figure 2**). More specifics on the biomarker search procedure are discussed below.

Figure 2. Search Biomarkers Screen

Fields to Search

A user can specify search terms for any or all of the following fields: Biomarker Name, Health Outcome Category, Health Outcome Description, Biomarker Type, Exposure, or Specimen Type. Fields with a down arrow on the right have drop-down menus from which the search term(s) can be selected. Any combinations of fields can be searched at the same time.

Search Strategy

The search procedure is designed to allow a search term or terms to be entered for any or all fields. The user can specify whether to search only abstracts that passed the review process (the default) or all abstracts in the database.

1. Searching Fields with Indexed Terms (Biomarker Name, Biomarker Type, Health Outcome Category, and Specimen Type)

These fields can be searched using any number of terms that are “OR’d” together within the field. For example, the user can search by more than one Biomarker Type (i.e., Exposure OR Effect). To search for any term(s) in these fields, the user clicks on the term using the upper left mouse button. The user chooses as many terms as desired in a given field. Selected terms will be highlighted in black. If the user accidentally selects a term that is not wanted, the term can be clicked on again to deselect that term.

2. Searching Fields Where the Terms are Entered By Hand (Health Outcome Description and Exposure)

These fields may also be searched using an “AND” feature, which is found in the drop-down menu in the upper right-hand corner of the field next to the field name. For multiple term searching, each of the terms must be typed on separate lines. To search using the “OR” feature, the drop-down menu must show “Match Any Phrase” (the default). To search using the “AND” feature, the drop-down menu option must be changed to “Match All Phrases.”

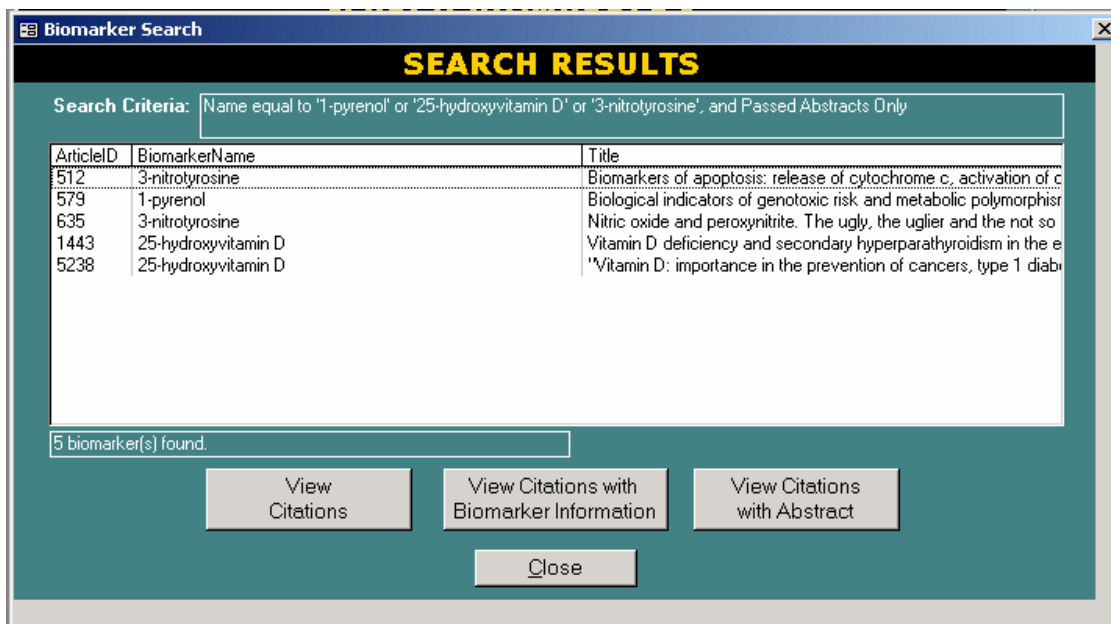
To initiate a new search, the user clicks the Clear button. Previous searches are not saved. The user can also specify whether to search only abstracts that passed the review process (the default) or all abstracts in the database. To search all records, the user unchecks the “Passed Articles Only” option at the bottom of the screen. However, in general, no biomarkers are listed for articles marked Cannot Ascertain or Fail.

Search Results and Reports

After entering the search terms, the user clicks the Search button. A Search Results table (**Figure 3**) will be displayed. The search criteria will be listed in the box at the top of the screen.

The following fields appear in the Results Table: Article ID, Biomarker Name, and Article Title. The Article ID is unique to the Biomarkers Database—it has no relation to PubMed identification numbers. Also, the same article will appear on multiple rows in the Search Results table if there are multiple biomarkers associated with the article. However, in the Reports section the citation will only appear once.

Figure 3. Biomarkers Search Results Screen



The Search Results screen allows the user to generate a report for (a) all titles in the list, (b) a highlighted title, or (c) multiple highlighted titles. The various reports include the following:

- Citations only
- Citations with biomarker information
- Citations with abstract

Prior to selecting the report to view, the references must be highlighted to be included in the report. For articles with multiple biomarkers recorded, all biomarkers must be highlighted for them to appear in the report “Citations with Biomarker Information.” In addition, for articles with many biomarkers recorded, the biomarker report will only include biomarkers meeting the search criteria. To view all biomarker information recorded for a reference, one uses either the Citations Search procedure or the Abstract Review Form (see **Section C**).

After the desired report is selected, the report will be displayed on the screen. To print the report, the user selects File, then Print from the menu bar at the top of the window. The standard Windows print menu will appear. Examples of reports are provided in **Appendix C**.

B. THE CITATIONS SEARCH

All of the citation information was obtained from PubMed. No revisions or additions were made to this information.

The Search Citations procedure is conducted on the citations compiled from the literature search. The search procedure is very similar to the method described under the biomarker search. The citations search procedure allows the user a search of multiple fields by defining a search term or terms for each field. **Figure 4** shows the Search Citations screen.

Figure 4. Search Citations Screen

Fields to Search

The user can specify search terms for any or all of the following fields: Title, Author, Journal, Year of Publication, or Keyword. Fields with down arrow keys (i.e., Journal, Year) have drop-down menus from which search term or terms can be selected.

Search Strategy

The search procedure is designed to allow a search term or terms to be entered for any or all fields. The user can also specify whether to search only abstracts that passed the review process (the default) or all abstracts in the database.

1. Searching Fields with Indexed Terms (Year)

This field can be searched using any number of years which are “OR’d” together within the field. For example, the user can search by more than one year. To search for any combination of years in the field, the user clicks on the year using the upper left mouse button. Any year or years can be selected in the field. Selected years will be highlighted in black. If the user selects a year by accident, the user can click on it again to deselect it.

2. Searching Fields Where the Terms Need to be Entered by Hand (Author and Keyword)

These fields can also be searched using an “AND” feature, which is found in the drop-down menu in the upper right-hand corner of the field next to the field name. For multiple term searching, each of the terms must be keyed in on separate lines. To search using the “OR” feature, the drop-down menu must show “Match Any Phrase”, which is the default. To search using the “AND” feature, the user changes the drop-down menu option to “Match All Phrases.”

3. Searching the Title and Journal Fields

The Title and Journal fields are the only fields that do not have an “AND” or “OR” search capability. To search by title, the user types in the word or words that should be included in a title. To search by journal name, the user clicks on the down arrow and the journal list will display. The desired journal can be selected by clicking on the name using the left mouse button.

Search Results and Reports

A Search Results table (see **Figure 5**) will be displayed to the user. The following fields appear in the results table: Article ID, Article Title, and Author.

Figure 5. Citations Search Results

ArticleID	Title	Authors
1959	Molecular epidemiology of human cancer risk. Gene-environment i	Vahakangas K;
2057	Myeloperoxidase promoter region polymorphism and lung cancer ris	Wu X;Schabath MB
2104	Prognosis of oral pre-malignant lesions: significance of clinical, hist	Reibel J;
2541	Osteopontin and colon cancer progression	Yeatman TJ;Chamb
4799	Epistatic effect of IL1A and IL4RA genes on the risk of atopy	Adjers K;Pessi T;Ka
4807	Effect of inhaled endotoxin on airway and circulating inflammatory i	Alexis NE;Eldridge M
4820	Metabolites of a tobacco-specific lung carcinogen in nonsmoking c	Anderson KE;Kliris J
4837	Rhabdomyosarcomagenesis-Novel pathway found	Asakura A;Rudnicki
4861	Polymorphisms in the interleukin-4 and interleukin-4 receptor alpha	Beghe B;Barton S;F
4884	Unexplained anaemia and failure to thrive as initial symptoms of inf	Blohm ME;Gobel U;
4998	Allergen-induced cytokine secretion in atopic and non-atopic asthm	Botcher MF;Björstr

The search results page allows the user to generate a report for (a) all titles in the list, (b) a highlighted title, or (c) multiple highlighted titles. The various reports include the following:

- Citations only
- Citations with biomarker information
- Citations with abstract.

Prior to selecting the report to view, the user must highlight the references to be included on the report. After the report to view has been selected, the report will be displayed on the screen. To print the report, the user selects File, then Print, from the menu bar at the top of the window. The standard Windows print menu will appear. Examples of reports are provided in **Appendix C**.

C. THE ABSTRACT REVIEW OPTION

The third main feature of the database is the ability to read (and for the editable database, to record) notes from a review of the article and/or its abstract. These review forms are similar to those used by project staff during abstract and article review.

There are three review forms:

- The Abstract Review form (**Figure 6**) is used to record whether the article may be relevant to this task. Every abstract in the biomarker database will have a Pass, Fail, or Cannot Ascertain result code on this form.
- The Biomarker Information form is used to record any biomarkers referenced in the abstract along with its health outcomes and some other information. Note: Some biomarkers were added to this form during the review of full articles.
- The Additional Information (Article Review) form was designed to record information obtained from reading the actual article. (Because few articles were read in full, this form was used very little and there is often little or no information recorded. However, the form has been retained in the database for possible future use.)

To read the review for an abstract, the user first selects a title of interest from the list of all citations in the database by clicking the left mouse button.

Figure 6. Abstract List for Review

ArticleID	Result	Title	Authors
1	Pass	Potential diagnostic aids for abnormal fatty	Ward,P.E.
2	Fail	Research on screening and diagnosis in au	Bristol-Power,M.M.
3	Pass	Genetic susceptibility to neurodevelopment:	Ryan,S.G.
4	Pass	Childhood risk factors for atopy and the imp	Wahn,U., von Muti
5	Pass	Immunology of respiratory syncytial virus in	Welliver,R.C.
6	Pass	Inflammatory markers in clinical practice	Wilson,N., Pederse
7	Pass	Sampling methods: urine/blood analysis	Koller,D.Y.
8	Pass	Gas analysis	de Jongste,J.C., Al

Record: 1 of 5889

Buttons: Open Review Form, Preview Abstract, Print Abstract, Close

After highlighting the title, the user clicks “Open Review Form.” The abstract review form will then be displayed (see **Figure 7**), showing the citation, abstract, and review.

Figure7. Abstract Review Form

From the Abstract Review form, the user views the biomarker information collected from the current reference (**Figures 8 and 9**) or goes to the Additional Information form to see the article review notes, if applicable (**Figure 10**). To view the biomarkers on one screen, the user clicks the “Display All BMs” button and it will display all the biomarkers entered for one citation (**Figure 9**).

Figure 8. Biomarker Information Form

Figure 9. Display All BMs Screen

Biomarker Citations with Biomarker Information					
Article ID:	5932	Language: English			
Authors:	Zanconato S;Carraro S;Corradi M;Alinovi R;Pasquale MF;Piacentini G;Zacchello F;Baraldi E;				
Title:	Leukotrienes and 8-isoprostane in exhaled breath condensate of children with stable and unstable asthma				
Journal:	J Allergy Clin Immunol				
Year:	2004	Volume:	113	Pages:	257 - 263
Biomarker Name: 8-isoprostane					
Type: Effect					
Exposure:					
Health Outcome Category: Cancer Respiratory Neurological Injury Other					
Health Outcome Description: Asthma					
Specimen Type: Exhaled air					
Biomarker Name: cysteinyl leukotrienes (CysLTs)					
Type: Not Specified					
Exposure:					
Health Outcome Category: Cancer Respiratory Neurological Injury Other					
Health Outcome Description: Asthma					
Specimen Type: Exhaled air					

Figure 10. Additional Information Form

Additional Information
ARTICLE REVIEW (Note: To expand box for writing, press Shift-F2)

Article ID: 1 Article Screen Result:
Reviewer: Reason for Failure:
Date Reviewed: Today

Study Species: Select: Human, Mammal, Blood, Urine, Saliva/buccal ce, Nasal lavage, Hair, Bone

Specimen Type: Specimen Degradation:
Biomarker Measurement Technique(s):
New Measurement Method(s) Being Explored:
Precision/Reliability/Required Sample:
Comments on Future Use(s): Disorders of neurodevelopment (attention deficit hyperactivity disorder,

Display Abstract Save Close

The Biomarker Information form (Figure 8) will appear blank upon opening it. The instructions now differ between the editable and non-editable versions of the database, so each is described separately below.

Non-editable Version

In the non-editable version of the database, to view the list of biomarkers discussed in the reference, the user clicks the “Display All BMs” button. The biomarker reports are displayed along with the full citation

(Figure 9). Note: The Save Record, New Record, and Get Record buttons are turned off in the non-editable version.

Editable Version

In the editable version of the database, to view the biomarker information available in the reference, the user clicks on the “Get Record” or “Display All BMs” button. The Get Record button will display a form with a list of the biomarkers discussed in the reference. Highlighting the biomarker of interest will bring up its information in the Biomarker Information form. To add a new biomarker to the reference (e.g., after reading the full article), the user fills in the blank form with all available information. To see the biomarkers added without editing them, the user clicks on “Display All BMs.”

In the editable version, the user may also add additional information to the Additional Information form. To do so, close the Biomarker Information form and open the Additional Information form.

Only the editable version of the database will allow the user to add a new reference to the database. The main menu of the editable database has an option to add a citation. This option will open a screen where the user can type the new citation and all of its accompanying information. Once the reference is added to the database, it cannot be edited or deleted.

ATTACHMENT 2
Pass/Fail Criteria for Abstract Review
Updated July 2004

Step 1: To pass the abstract review, the abstract must

- 1) Describe research conducted on animals during any life stage.
- 2) Describe one or more biomarkers, as defined below:

Biomarker is defined as a cellular, biochemical, molecular, or tissue alteration that is measurable in biological media, such as human tissues, cells or fluids; or the product of an interaction between a xenobiotic agent and some target molecule. Biomarkers could fall into one of the following three categories:

Biomarker of Exposure – concentrations of the exogenous parent chemical, its metabolites, or reaction products in body fluids or tissues.

Biomarker of Effect – measures of disease progression such as antigen secretion, gene suppression, DNA adducts, not including biomarkers measured in tumor tissue.

Biomarker of Susceptibility – particular genotype or polymorphism or precursor disease.

- 3) May describe any of the topics present in the YES column but not in the NO column of the table below.

YES	NO
<ul style="list-style-type: none"> ▪ Investigation of specific genes ▪ pre-cancerous lesions or polyps ▪ diagnostic markers ▪ exogenous parent chemical in body fluids or tissues ▪ metabolites in body fluids or tissues ▪ reaction products in body fluids or tissues ▪ antigen secretion ▪ gene suppression ▪ DNA adducts ▪ susceptible genotype ▪ susceptible polymorphism ▪ precursor disease 	<ul style="list-style-type: none"> ▪ markers of prognosis only ▪ medical or clinical test results ▪ behavioral/ cognitive functioning test results ▪ physical measurements such as birth weight ▪ biomarkers measured in tumor tissue

- 4) Describe an adverse health outcome.

Step 2: Each abstract requires the entry of pass/fail/cannot ascertain into the Abstract Review Form of the Biomarkers Database. If the abstract meets all of the criteria, a Biomarker Information Form is completed.

APPENDIX A
PubMed Search String Details and Limitations

Category	Search Terms and PubMed Search Details	Limitations
General	(biomarker* or biological Markers [MESH] AND exposure AND environmental pollution (" biological markers" [Mh] OR biomarker [TW]) AND exposure[ALL]) AND ("environmental pollution"[MeSH Terms] OR environmental pollution[Text Word])	7/03-Present; English, Review
	molecular epidemiology ("epidemiology, molecular"[Mh] OR molecular epidemiology[TW])	7/03-Present; English, Review
	(biomonitor OR "environmental monitoring"[mh]) AND expos* (biomonitor[All Fields] OR "environmental monitoring"[MeSH Terms]) AND (expos[All Fields])	7/03-Present; English, Review
	genetic marker AND (biomarker OR "biological markers"[MAJR]) (genetic marker[ALL] OR genetic markers[ALL]) OR genetic markers/analysis[ALL] OR genetic markers/blood[ALL] OR genetic markers/genetics[ALL] OR genetic markers/immunology[ALL] OR genetic markers/physiology[ALL] OR genetic markers/urine[ALL] AND ((biomarker[ALL] OR biomarker/polymerase[ALL]) OR biomarkers[ALL]) OR "biological markers"[MAJR])	7/03-Present; English, Review
	predisposition to disease AND biomarker ("disease susceptibility"[Mh] OR predisposition[TW]) AND ("disease"[Mh] OR disease[TW])) AND ((biomarker[ALL] OR biomarker/polymerase[ALL]) OR biomarkers[ALL])) OR "biological markers"[MAJR])	7/03-Present; English, Review
	metabolit* AND expos* (metabolit* [ALL]) AND (expos*[ALL])	7/03-Present; English, Review
	fetus AND biomarker ("fetus"[Mh] OR fetus[TW]) AND ("biological markers"[Mh] OR biological marker[TW])	7/03-Present; English, Review
	pregnancy complications AND biomarker ("pregnancy complications"[Mh] OR pregnancy complications[TW]) AND ("biological markers"[Mh] OR biomarker[TW])	7/03-Present; English, Review
	pregnancy outcome AND biomarker ("pregnancy outcome"[Mh] OR pregnancy outcomes[TW]) AND ("biological markers"[Mh] OR biomarker[TW])	7/03-Present; English, Review

Category	Search Terms and PubMed Search Details	Limitations
Exposure	<p>(pesticides[mh] OR pesticide*) AND ("biological Markers"[MESH] OR biomarker) ("pesticides"[Mh] OR (pesticide[ALL] OR pesticide/animal[ALL]) OR pesticide/herbicide[ALL]) OR pesticide/m2[ALL]) OR pesticide/solvent[ALL]) OR pesticideformulating[ALL]) OR pesticides[ALL]) OR pesticides/analysis[ALL]) OR pesticides/blood[ALL]) OR pesticides/chemistry[ALL]) OR pesticides/classification[ALL]) OR pesticides/commodities[ALL]) OR pesticides/economics[ALL]) OR pesticides/fertilisers[ALL]) OR pesticides/fertilizer[ALL]) OR pesticides/history[ALL]) OR pesticides/immunology[ALL]) OR pesticides/metabolism[ALL]) OR pesticides/metabolites[ALL]) OR pesticides/pharmacokinetics[ALL]) OR pesticides/pharmacology[ALL]) OR pesticides/poisoning[ALL]) OR pesticides/standards[ALL]) OR pesticides/toxicity[ALL]) OR pesticides/urine[ALL]) OR pesticides/weedicides[ALL])) AND "biological Markers"[MH]) OR (biomarker[ALL] OR biomarker/polymerase[ALL]) OR biomarkers*[ALL])</p>	7/03-Present; English,
	<p>effect AND biomarker AND exposure (effect[ALL] AND ("biological markers" [Mh] OR biomarker[TW]) AND exposure[ALL])</p>	7/03-Present; English, Review
	<p>Susceptibility AND biomarker AND exposure ("disease susceptibility"[Mh] OR Susceptibility[TW]) AND ("biological markers"[Mh] OR biomarker [TW]) AND exposure[ALL])</p>	7/03-Present; English, Review
	<p>("air pollution"[MESH] OR "air pollutants" [MESH] OR air pollut*) AND ("biological markers" [MESH] Or biomarkers*) ("air pollution"[MH] OR "air pollutants"[MH]) OR (air pollutant[ALL] OR air pollutants[ALL]) OR air pollutants/analysis[ALL]) OR air pollutants/blood[ALL]) OR air pollutants/chemistry[ALL]) OR air pollutants/classification[ALL]) OR air pollutants/economics[ALL]) OR air pollutants/history[ALL]) OR air pollutants/immunology[ALL]) OR air pollutants/metabolism[ALL]) OR air pollutants/pharmacokinetics[ALL]) OR air pollutants/pharmacology[ALL]) OR air pollutants/poisoning[ALL]) OR air pollutants/standards[ALL]) OR air pollutants/toxicity[ALL]) OR air pollutants/urine[ALL]) OR air polluted[ALL]) OR air polluting[ALL]) OR air pollution[ALL]) AND "biological markers"[ALL])</p>	7/03-Present; English
Asthma	<p>asthma AND biomarker ("asthma"[Mh] OR asthma[TW]) AND ("biological markers"[Mh] OR biomarker[TW])</p>	7/03-Present; English,
	<p>respiratory health AND biomarker (respiratory[ALL] AND ("health"[Mh] OR health[TW]) AND ("biological markers"[Mh] OR biomarker [TW])</p>	7/03-Present; English,
	<p>asthma AND biomarker AND exposure asthma AND exposure[ALL] AND biomarker* OR biological Markers [MH]</p>	7/03-Present; English,
	<p>("respiratory tract diseases"[MAJR] OR asthma) AND ("biological markers"[MESH] OR biomarker) ("respiratory tract diseases"[MAJR] OR ("asthma"[Mh] OR asthma[TW])) AND "biological Markers"[MH]) OR ((biomarker[ALL] OR biomarker/polymerase[ALL]) OR biomarkers[ALL])</p>	7/03-Present; English,

Category	Search Terms and PubMed Search Details	Limitations
Cancer	cancer AND biomarker ("neoplasms"[Mh] OR cancer [TW]) AND ("biological markers"[Mh] OR biomarker[TW])	7/03-Present; English, Review
	cancer AND biomarker AND pregnancy (biomarker* OR biological markers) AND (cancer OR neoplasms) AND pregnancy	7/03-Present; English, Review
	cancer AND biomarker AND pregnancy AND exposure (biomarker* OR biological markers) AND (cancer OR neoplasms) AND pregnancy	7/03-Present; English, Review
Neurodevelopmental Disorders	autism AND biomarker ("autistic disorder"[Mh] OR autism[TW]) AND ("biological markers [Mh] OR biomarker[TW])	7/30-Present; English,
	neurodevelopmental disorders AND exposure (neuro[ALL] AND ("developmental disabilities"[Mh] OR developmental disorders[TW]) AND exposure[ALL])	7/03-Present; English,
	developmental disability AND biomarker ("developmental disabilities"[Mh] OR Developmental disabilities[TW]) AND ("biological markers"[Mh] OR biomarker[TW])	7/03-Present; English,
	(neurotoxicity OR neurotoxicology) AND biomarker (("neurotoxicity syndromes"[Mh] OR neurotoxicity[TW]) OR neurotoxicology[ALL]) AND ("biological markers"[Mh] OR biomarker[TW])	7/03-Present; English, Review
	(neurological development OR "nervous system/growth and development[mh]) AND biomarker (neurological[ALL] AND (("growth and development"[mh] OR "human development"[Mh]) OR development[TW])) AND ("biological markers"[Mh] OR biomarker[TW])	7/03-Present English, Review
Injury	injury and biomarker ("wounds and injuries"[Mh] OR injury [TW]) AND ("biological markers" [Mh] OR biomarker [TW])	7/03-Present; English, Review
	injur* AND exposure AND adverse effects (Wounds and Injuries [MH] OR injur*[ALL]) AND exposure[ALL]) AND ("adverse effects"[Mh] OR adverse effects[TW])	7/03-Present; English, Review
	biological marker [MESH] coordination AND exposure ("biological markers"[Mh] AND ("organization and administration"[Mh] OR coordination[TW])) AND exposure[ALL])	7/03-Present English, Review
	(biological marker [MESH] or biomarker*) AND impulsive behavior ("biological markers"[Mh] OR ((biomarker[ALL] OR biomarker/polymerase[ALL]) OR biomarkers[ALL])) AND ("impulsive behavior"[Mh] OR impulsive behavior[TW])	7/03-Present English, Review

Category	Search Terms and PubMed Search Details	Limitations
Miscellaneous	HOXA gene OR “homeodomain proteins”[mh] OR “hoxa proteins”[mh]	7/03-Present; English, Review
	GABA AND (biomarker OR marker)	7/03-Present; English, Review
		7/03-Present; English, Review
	VIP OR “vasoactive intestinal peptide”[mh]	7/03-Present; English, Review
	Purkinje cells	7/03-Present; English, Review
Ubiquitin		7/03-Present; English, Review
	Saliva AND (biomarker OR marker)	7/03-Present; English, Review

Meconium

APPENDIX B Biomarker Definitions

Biomarker. A biomarker is defined as a cellular, biochemical, or molecular (or tissue) alteration that is measurable in biological media, such as human tissues, cells, or fluids; or the product of an interaction between a xenobiotic agent and some target molecule. Biomarkers include specific genes, pre-cancerous lesions or polyps, and diagnostic markers.

Biomarkers do not include markers of prognosis only, medical or clinical test results (such as from sepsis workups, bone mineral density, EEGs, or x-ray analysis), behavioral/cognitive functioning test results, or growth or other physical measurements or observations (such as birth weight, length, head circumference, or fingerprint ridge count).

Biomarkers of Exposure. Biomarkers of exposure include concentrations of the exogenous parent chemical, its metabolites, or reaction products in body fluids or tissues (e.g., blood lead, etc.). *Bioindicators* reflect only the presence or absence of a substance. *Biomonitoring* provides for regular surveillance and quantification of the amount of substance present.

Biomarkers of Effect. Biomarkers of effect are measures of disease progression (e.g., biomarkers of early loss of pregnancy, benzo-pyrene-DNA adducts, antigen production, tumor secretions, gene suppression, etc.). Biomarkers measured in tumor tissue were not included, as the disease is diagnosed prior to the biomeasure, and the biomarker is used to determine prognosis rather than effect.

Biomarkers of Susceptibility. Biomarkers of susceptibility include the detection of a particular genotype or polymorphism (such as genetic markers of cancer susceptibility), or may be a precursor disease, such as precancerous colonic polyps. They may indicate the presence of or potential for subclinical disease or may indicate a potential protection against negative health effects of the exposure.

APPENDIX C Database Reports

The search procedures can generate three types of reports to display the search results: (a) a report with citations only, (b) a report with citations and biomarker information, and (c) a report with citations and abstracts.

The first report lists only the basic citation information for the search results (**Figure C-1**).

Figure C-1

Biomarker Citations			
Article ID:	989	Language:	English
Authors:	Blum,H.E.		
Title:	Hepatocellular carcinoma susceptibility markers		
Journal:	IARC Sci.Publ.		
Year:	Volume:	Pages:	
2001	154	241 - 244	
Article ID:	1302	Language:	English
Authors:	Nair,J., Bartsch,H.		
Title:	Metabolic polymorphisms as susceptibility markers for lung and oral cavity cancer		
Journal:	IARC Sci.Publ.		
Year:	Volume:	Pages:	
2001	154	271 - 290	
Article ID:	1893	Language:	English
Authors:	Czernin,J., Phelps,M.E.		
Title:	Positron emission tomography scanning: current and future applications		
Journal:	Annu.Rev.Med.		
Year:	Volume:	Pages:	
2002	53	89 - 112	
Article ID:	1895	Language:	English
Authors:	Rennen,H.J., Corstens,F.H., Oyen,W.J., Boerman,O.C.		
Title:	New concepts in infection/inflammation imaging		
Journal:	Q.J.Nucl.Med.		

The second report lists the basic citation information along with biomarker information recorded on this article. For the Citation Search, the report will include ALL biomarkers identified in the abstract. For the biomarker search, the report will only include the biomarkers that met the search criteria (e.g., those biomarkers whose name contains the term “CYP”). See **Figure C-2**.

Figure C-2

Biomarker Citations with Biomarker Information			
Article ID:	4815	Language:	English
Authors:	Ameen M;Musthapa S;Ahmad I;Ansari F A;Baig M A;Rahman Q;		
Title:	Alteration in cellular and biochemical markers of pulmonary toxicity in rat lung exposed to carpet dusts		
Journal:	Inhal Toxicol		
Year:	2003	Volume:	15
		Pages:	1119 - 1131
Biomarker Name: CYP (P450)			
Type: Exposure			
Exposure: Carpet dust			
Health Outcome Category: <input type="checkbox"/> Cancer <input checked="" type="checkbox"/> Respiratory <input type="checkbox"/> Neurological <input type="checkbox"/> Injury <input type="checkbox"/> Other			
Health Outcome Description: Pulmonary damage			
Specimen Type: Organ tissue			

The last report lists the basic citation information along with the abstract for the article (Figure C-3).

Figure C-3

Biomarker Citations with Abstract	
Article ID:	4815
Language:	English
Authors:	Ameen M;Musthapa S;Ahmad I;Ansari F A;Baig M A;Rahman Q;
Title:	Alteration in cellular and biochemical markers of pulmonary toxicity in rat lung exposed to carpet dusts
Journal:	Inhal Toxicol
Year:	2003
Volume:	15
Pages:	1119 - 1131
Abstract	<p>"Epidemiological studies of workers in weaving units in carpet industries have shown relationships between the airborne dust concentrations and pulmonary ill health. Therefore, to predict the health risk of carpet weavers, this preliminary experiment was conducted to evaluate the effect of carpet dust (knotted, tufted) on cellular and biochemical mediators considered as potential biological markers of lung injury. Lung cytoplasmic (lactate dehydrogenase, LDH), lysosomal (acid phosphatase, ACP), type II (alkaline phosphatase, ALP) and Clara-cell marker enzymes (gamma-glutamyl transferase, GGT) were monitored in rat cell-free lung lavage (BAL) during postexposure days 1, 4, 8, and 16. Furthermore, lung microsomal cytochrome P-450 (CYP 450) and Clara-cell secretory protein (CC16) content in BAL was also evaluated. These pulmonary marker enzymes were significantly elevated during the postexposure period over the respective untreated control; however, tufted carpet dust shows more responses than knotted carpet dust. Lung CYP 450 content was reduced significantly at early days; the pattern shows the reoccurrence of CYP 450 content in the later stage of postexposure to carpet dust. Clara-cell secretory protein in BAL shows decline in the carpet-treated group; however, tufted carpet shows more decline than knotted carpet. Thus, reduction in CC16 level may have important implication in the development of chronic lung inflammation and diseases. Present investigation found that modulation of these cellular marker enzymes is clear evidence of pulmonary damage caused by exposure to carpet dust"</p>
Keywords:	"Acid Phosphatase;metabolism;Animals;Biological Markers;analysis;Bronchoalveolar Lavage Fluid;chemistry;Comparative Study;Cytochrome P-450 Enzyme System;Dust;Electrophoresis;Polyacrylamide Gel;Environmental Exposure;adverse effects;Floors and Floorcoverings;L-Lactate Dehydrogenase;Lung;enzymology;pathology;Macrophages;Alveolar;Male;Microsomes;Proteins;Rats;Support,Non-U.S.Gov't;Time Factors;"

