

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

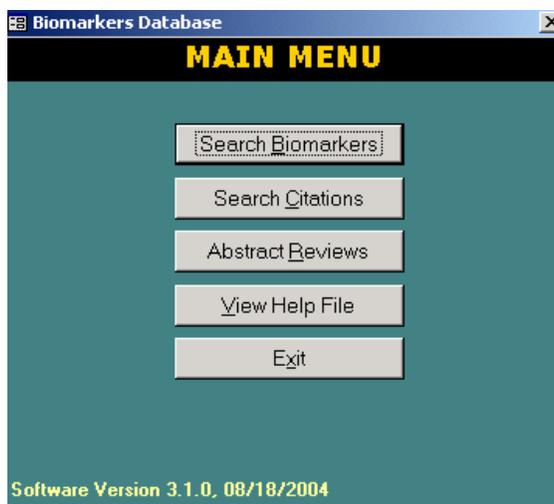
| Category | Keyword Search Strings | Limitations |
|-------------------------------------|---|---|
| General | <ol style="list-style-type: none"> 1. biomarker AND exposure AND environmental pollution. 2. molecular epidemiology 3. (biomonitor or environmental monitoring) AND exposure 4. genetic marker AND biomarker 5. predisposition to disease AND biomarker 6. metabolite AND exposure 7. fetus AND biomarker 8. pregnancy complication AND biomarker | <p>7/1/03-6/24/04, English, Review “</p> <p>“</p> <p>“</p> <p>“</p> <p>“</p> <p>“</p> |
| Exposure | <ol style="list-style-type: none"> 9. pesticides AND biomarker 10. air pollution AND biomarker 11. effect biomarker AND exposure 12. susceptibility biomarker AND exposure | <p>7/1/03-6/24/04, English, Review “</p> <p>“</p> |
| Asthma | <ol style="list-style-type: none"> 13. asthma AND biomarker 14. respiratory health AND biomarker 15. asthma AND biomarker AND exposure 16. respiratory tract diseases AND biomarker | <p>7/1/03-6/24/04, English “</p> <p>“</p> <p>“</p> |
| Cancer | <ol style="list-style-type: none"> 17. cancer AND biomarker 18. cancer AND biomarker AND pregnancy 19. cancer AND biomarker AND pregnancy AND exposure | <p>7/1/03-6/24/04, English, Review “</p> <p>“</p> |
| Neurodevelopmental Disorders | <ol style="list-style-type: none"> 20. autism AND biomarker 21. neurodevelopmental disorder AND exposure 22. developmental disability AND biomarker 23. neurotoxic* AND biomarker 24. neurological development AND biomarker | <p>7/1/03-6/24/04, English, “</p> <p>“</p> <p>“</p> <p>“</p> <p>“</p> |
| Injury | <ol style="list-style-type: none"> 25. injury AND biomarker 26. injury AND exposure AND adverse effects 27. coordination AND biomarker AND exposure 28. impulsive behavior AND biomarker AND exposure | <p>7/1/03-6/24/04, English, Review “</p> <p>“</p> <p>“</p> |
| Miscellaneous | <ol style="list-style-type: none"> 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) | <p>7/1/03-6/24/04, English, Review “</p> <p>“</p> <p>“</p> <p>“</p> <p>“</p> <p>“</p> |

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



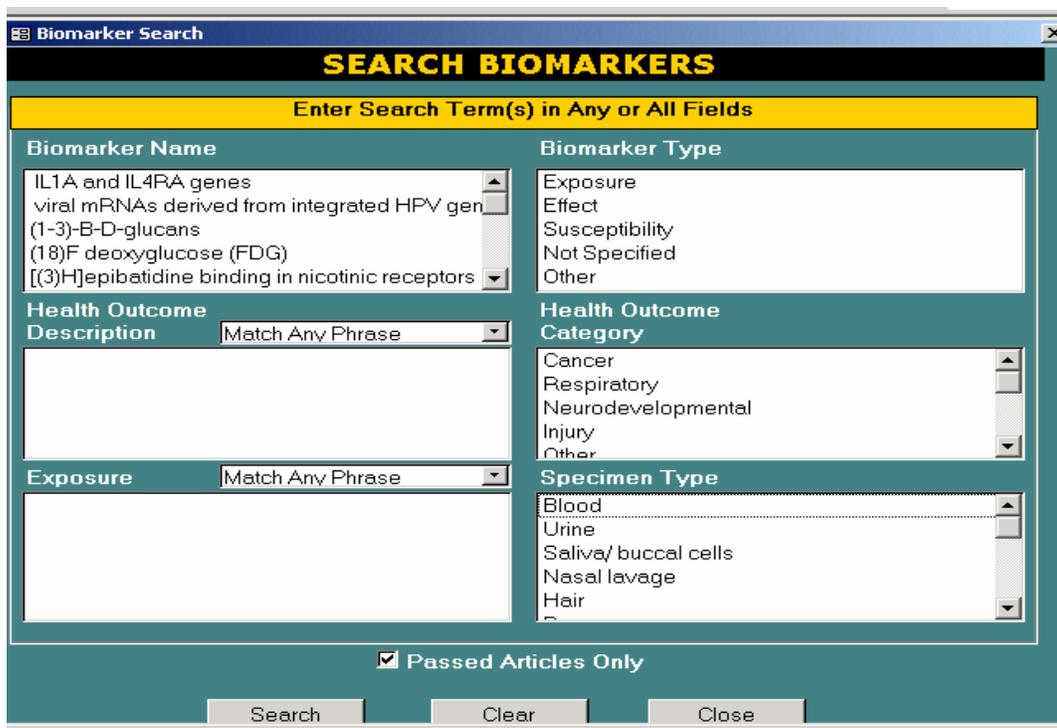
Two versions of the Biomarkers Database were provided to EPA. One version allows the user to view the contents of the database without making any modifications or additions. The other "editable" version allows users to modify the database's contents and to add additional references. Both versions of 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.”

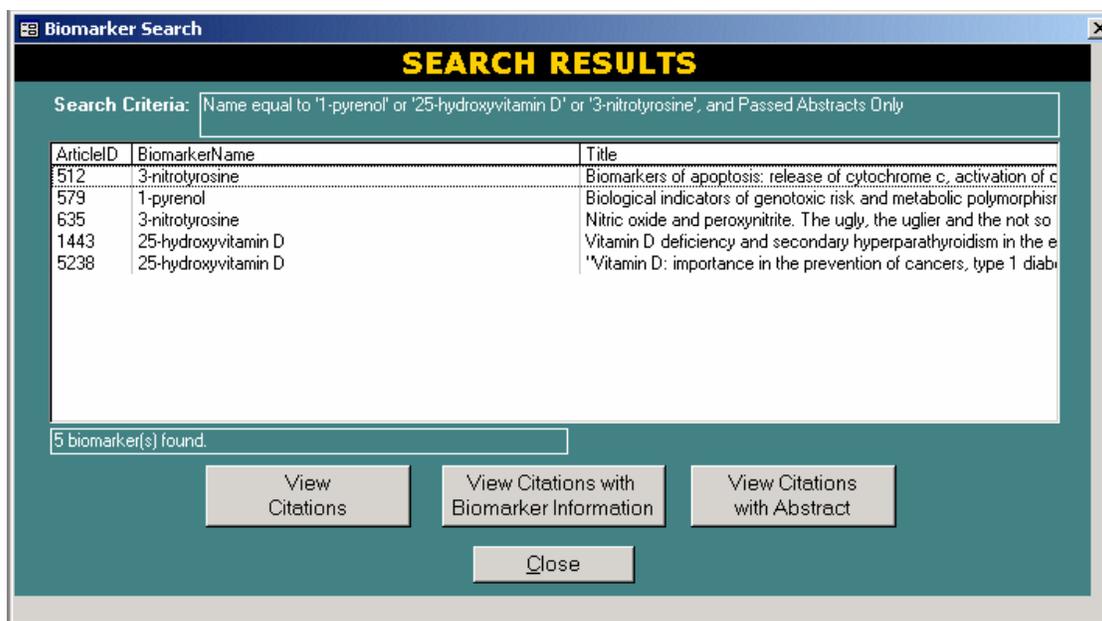
To initiate a new search, the user clicks the Clear button. Previous searches are not saved. The user can also specify whether to search only abstracts that passed the review process (the default) or all abstracts in the database. To search all records, the user unchecks the “Passed Articles Only” option 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

The screenshot shows a software window titled "Citations" with a close button in the top right corner. The window's main content area has a dark teal background. At the top of this area is a black banner with the text "SEARCH CITATIONS" in yellow. Below the banner is a yellow horizontal bar containing the instruction "Enter Search Term in Any or All Fields". The search form consists of several fields: "Title" (a simple text input), "Author" (a text input with a dropdown menu set to "Match Any Phrase"), "Journal" (a dropdown menu), "Year" (a list box showing "2004", "2003", and "2002"), and "Keyword" (a text input with a dropdown menu set to "Match Any Phrase"). At the bottom of the form is a checked checkbox labeled "Passed Abstracts Only". Below the form are three buttons: "Search", "Clear", and "Close".

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; |
| 4898 | Allergen-induced cytokine secretion in atopic and non-atopic asth | Rotcher 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

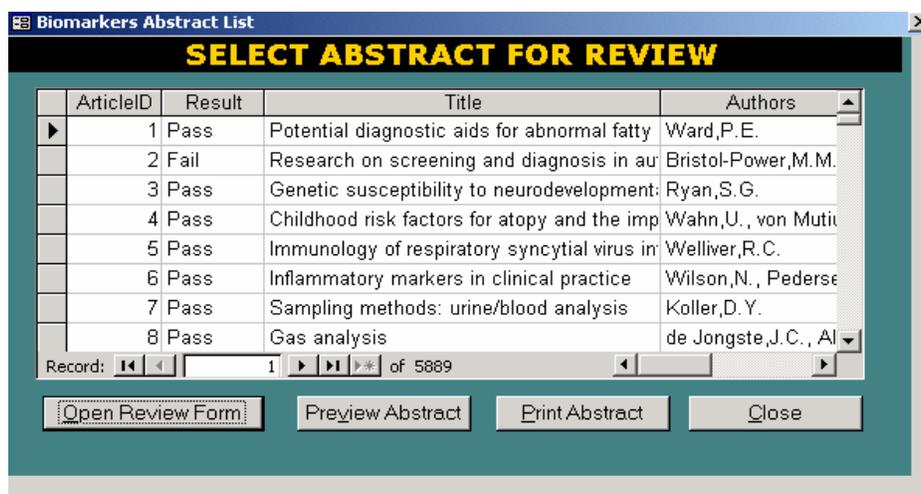
The third main feature of the database is the ability to read (and for the editable database, to record) notes from a review of the article and/or its abstract. These review forms are similar to those used by project staff during abstract and article review.

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



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

The screenshot shows a window titled "Abstract Review" with a dark blue header. The main content is divided into two sections: "ABSTRACT SUMMARY" and "ABSTRACT REVIEW".

ABSTRACT SUMMARY

- Article ID: 5737
- Title: "Family, twin, and adoption studies of bipolar disorder"
- Author(s): Smoller JW; Finn CT;
- Journal: Am J Med Genet Year: 2003
- Keywords: Adoption; Biological Markers; Bipolar Disorder; genetics; psychology; Genetic Predisposition to
- Abstract: "Family, twin, and adoption studies have been essential in defining the genetic epidemiology of bipolar disorder over the past several decades."

ABSTRACT REVIEW

- Reviewer: EM-RTI
- Date Screened: 8/9/2004 Today
- Screen Result: Pass
- Reason for Failure: (empty dropdown)
- Publication Type: Review article, chapter - general

Buttons at the bottom: Save, Display Abstract, Biomarker Info, Additional Info, Close.

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

The screenshot shows a window titled "Biomarker Form" with a dark blue header. The main content is a form titled "BIOMARKER INFORMATION" with "Article ID: 1" in the top right corner.

BIOMARKER INFORMATION

- Biomarker Name: (dropdown)
- Biomarker Type?: (dropdown)
- Exposure Indicated: (text input)
- Health Outcome Category: Cancer Respiratory Neurodevelopmental Injury Other
- SPECIFY Health Outcome: (text input)
- Intermediate/ Subclinical Endpoint: (dropdown)
- Specimen Type: (text input) Blood, Urine, Saliva/ buccal cells (dropdown)

Buttons at the bottom: Display Abstract, Display All BMs, Save Record, New Record, Get Record, Delete Record, Close 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

ARTICLE REVIEW (Note: To expand box for writing, press Shift-F2)
Article ID: 1 **Article Screen Result:** [dropdown]
Reviewer: [dropdown] **Reason for Failure:** [dropdown]
Date Reviewed: Today

| | | | | |
|-------------------------------|--|--|--|--|
| Study Species: | | Select: | Specimen Degradation: | |
| Specimen Type: | | Human Mammal Blood Urine Saliva/ buccal ce Nasal lavage Hair Bone | Biomarker Measurement Technique(s): | |
| Invasive/ Noninvasive: | | | New Measurement Method(s) Being Explored: | |
| Specimen Sample Size: | | | Precision/ Reliability/ Required Sample: | |
| Collection Conditions: | | | Comments on Future Use(s): | Disorders of neurodevelopment (attention deficit hyperactivity disorder, |

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.

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 | (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]) | 7/03-Present; English, |
| | effect AND biomarker AND exposure (effect[ALL] AND ("biological markers" [Mh] OR biomarker[TW]) AND exposure[ALL]) | 7/03-Present; English, Review |
| | Susceptibility AND biomarker AND exposure ("disease susceptibility"[Mh] OR Susceptibility[TW]) AND ("biological markers"[Mh] OR biomarker [TW]) AND exposure[ALL]) | 7/03-Present; English, Review |
| | ("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]) | 7/03-Present; English |
| Asthma | asthma AND biomarker ("asthma"[Mh] OR asthma[TW]) AND ("biological markers"[Mh] OR biomarker[TW]) | 7/03-Present; English, |
| | respiratory health AND biomarker (respiratory[ALL] AND ("health"[Mh] OR health[TW]) AND ("biological markers"[Mh] OR biomarker [TW]) | 7/03-Present; English, |
| | asthma AND biomarker AND exposure asthma AND exposure[ALL] AND biomarker* OR biological Markers [MH] | 7/03-Present; English, |
| | ("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, |

| 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 |
| | Ubiquitin | 7/03-Present; English, Review |
| | VIP OR “vasoactive intestinal peptide”[mh] | 7/03-Present; English, Review |
| | Purkinje cells | 7/03-Present; English, Review |
| | Meconium | 7/03-Present; English, Review |
| | Saliva AND (biomarker OR marker) | 7/03-Present; English, Review |

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, precancerous 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.

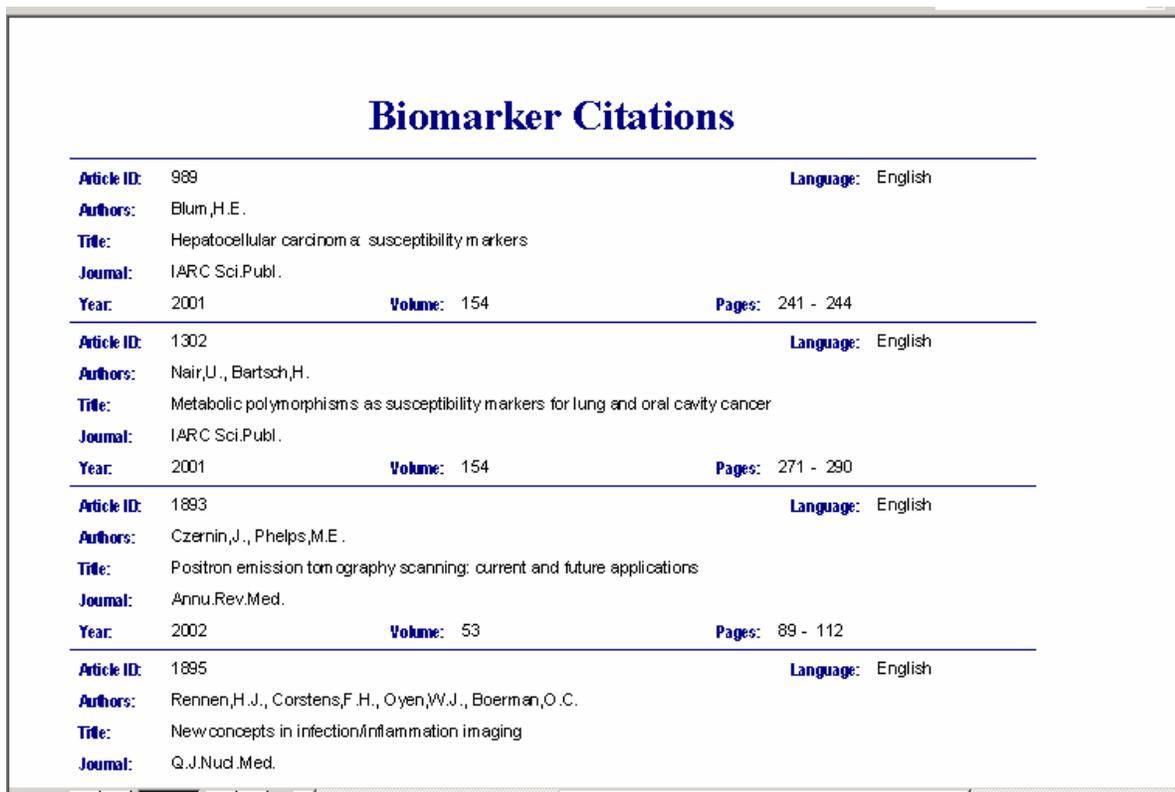
Biomarkers of Susceptibility. Biomarkers of susceptibility include the detection of a particular genotype or polymorphism (such as genetic markers of cancer susceptibility), or may be a precursor disease, such as precancerous colonic polyps. They may indicate the presence of or potential for subclinical 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: | 2001 | Volume: | 154 | Pages: | 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: | 2001 | Volume: | 154 | Pages: | 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: | 2002 | Volume: | 53 | Pages: | 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 MA;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: Cancer Respiratory Neurological Injury 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 MA;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

"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 CYP450 content was reduced significantly at early days; the pattern shows the reoccurrence of CYP450 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"

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;"
