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ATTACHMENT 1
LITERATURE SEARCH STRATEGY

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OBJECTIVES

1. Identify all English language literature providing relevant human data for patch, plaster or poultice formulations of topical anesthetic counterirritants. Specific areas of interest included safety/toxicity, efficacy, and dermal absorption.
2. Identify any animal literature in which the topical anesthetic counterirritants were studied under occlusive conditions for purposes of measuring transdermal absorption.

LIMITATIONS

The formulations specified in our search for objective 1 were limited to patch, plaster and/or poultice. Analgesics were limited to camphor, menthol, methyl salicylate, and capsaicin (also referred in older literature as capsicum). Formulations were not specified for objective 2.

SEARCH METHODOLOGY

Five major databases (listed below) were selected for this search. For objective 1, the search was limited to human data; for objective 2, the search was limited to animal data. The five databases searched have somewhat different years of coverage, beginning in the 1960's or 1970's, and continuing to date (see description of individual databases below). When it became evident that only limited relevant literature existed, the searches were conducted without further limiting the dates.

The search string for objective 1 was as follows:
Human AND (methyl salicylate OR camphor OR menthol OR capsicum OR capsaicin)
AND (patch OR plaster OR poultice).

The search string for objective 2 was as follows:
Animal AND (methyl salicylate OR camphor OR menthol OR capsicum OR capsaicin)
AND (absorp(tion) AND (occlusion)).

A preliminary attempt was made to characterize the search findings of objective 1 using key words including "skin reaction", "repeated insult patch test", "dermal absorption", "hypersensitivity", and several other topics of interest. However, this process did not markedly narrow the search findings, and therefore all literature from the initial search string was evaluated.

Based on the scant quantity of literature identified by these searches (104 independent citations for the human search, 135 for the animal search), we reviewed each of their abstracts. Decisions to retrieve and evaluate specific papers were made after judging the likelihood that information relevant to our specific objectives would be present.

SUMMARY OF FINDINGS

Search 1. Out of thousands to greater than a million citations identified for each counterirritant ingredient or each formulation type, only 104 citations matched the entire search string. Upon review of their abstracts, only a minority of citations contained data relevant to our specific questions. Approximately 20 to 25 references were ordered, and only had relevant data.

Search 2. Out of thousands to greater than a million citations identified for each counterirritant ingredient or the key words for absorption or occlusion, only 135 citations matched the entire search string. From review of their abstracts, only two citations appeared to possibly provide data about transdermal absorption under occlusive conditions.

DATABASES UTILIZED FOR THE SEARCH

Biosis: BIOSIS Previews[®] contains citations from *Biological Abstracts*[®] (BA), and *Biological Abstracts/Reports, Reviews, and Meetings*[®] (BA/RRM) (formerly *BioResearch Index*[®]), the major publications of BIOSIS[®]. Together, these publications constitute the major English-language service providing comprehensive worldwide coverage of research in the biological and biomedical sciences. *Biological Abstracts* includes approximately 350,000 accounts of original research yearly from nearly 6,000 primary journal and monograph titles. *Biological Abstracts/RRM* includes an additional 200,000+ citations a year from meeting abstracts, reviews, books, book chapters, notes, letters, selected institutional and government reports, and research communications. U.S. patents are included from 1986 through 1989 and from 1994 to the present.

Embase: EMBASE has long been recognized as an important, comprehensive index of the world's literature on human medicine and related disciplines. About 450,000 records are added annually, in recent years over 80% of which contain abstracts. Each record is classified and indexed by medical research specialists who assign terms and codes in accordance with Emtree, a highly developed classification schedule and controlled vocabulary, consisting of over 45,000 terms and nearly 190,000 synonyms. In recent years, EMBASE provides access to periodical articles from more than 3,700 primary journals from approximately 70 countries. An additional 350 journals are screened for drug articles.

Medline: MEDLINE (Medical Literature, Analysis, and Retrieval System Online), produced by the U.S. National Library of Medicine (NLM), is the U.S. National Library of Medicine's (NLM) premier bibliographic database that contains more than 12 million references to journal articles in life sciences with a concentration on biomedicine. The broad coverage of the database includes basic biomedical research and the clinical sciences since 1966 including nursing, dentistry, veterinary medicine, pharmacy, allied health, and pre-clinical sciences. MEDLINE also covers life sciences that are vital to biomedical practitioners, researchers, and educators, including some aspects of biology,

environmental science, marine biology, plant and animal science as well as biophysics and chemistry. Increased coverage of life sciences began in 2000. The database also includes records that cover the field of space life science and date from 1961 to present. Examples of these records include basic bone and muscle physiology, psychological effects of isolation, and gravitational effects on plants.

Pascal: PASCAL is produced by the Institut de l'Information Scientifique et Technique (INIST) of the French National Research Council (CNRS). It provides access to the world's scientific and technical literature and includes about 450,000 new citations per year. Available in machine-readable form since 1973, PASCAL corresponds to the print publication *Bibliographie internationale* (previously *Bulletin signaletique*).

Each citation includes the article's original title, and, in most cases, a French translated title; for material since 1973, an English translated title is also provided. Most abstracts are in French. Analyzed documents come from all over the world, in 100 different languages. French journals are particularly well represented. The file's breakdown by language is as follows: English 63%, French 12%, Russian 10%, German 8%, and other languages 7%.

SciSearch: SciSearch[®]: A Cited Reference Science Database is an international, multidisciplinary index to the literature of science, technology, biomedicine, and related disciplines produced by the Institute for Scientific Information[®] (ISI[®]). SciSearch contains all of the records published in the *Science Citation Index*[®] (SCI[®]), plus additional records from the *Current Contents*[®] publications.

SciSearch indexes all significant items (articles, review papers, meeting abstracts, letters, editorials, book reviews, correction notices, etc.) from approximately 4,500 major scientific and technical journals. Some 3,800 of these journals are further indexed by the references cited within each article, allowing for citation searching. An additional 700 journals indexed have been drawn from ISI Current Contents[®] series of publications.