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Priority-Based Assessment of Food Additives Database of the U.S. Food and Drug Administration Center for Food Safety and Applied Nutrition

by R. Daniel Benz* and Hiltje Irausquin*

The priority-based assessment of food additives (PAFA) is a database maintained by the U.S. Food and Drug Administration (FDA) Center for Food Safety and Applied Nutrition. PAFA contains extensive administrative, chemical, and toxicological information on 1685 regulated direct food additives. The database also has limited administrative and chemical information on an additional 1236 direct additives. The total 2921 substances represent everything added to food in the United States. PAFA contains up to 150 different kinds of information about each chemical. Administrative and chemical information includes Chemical Abstracts Service Registry numbers, Code of Federal Regulations citations, the annual usage and estimated daily U.S. human consumption, the Joint Committee on Food Additives Allowable Daily Intakes, the FDA Redbook structure categories of the chemicals, and their technical effects. Toxicology information shows the type of studies done for each chemical, the species of animals tested, the toxicological effects observed and the sites where they were seen, the lowest doses that cause a toxicological effect in each study, a source citation, and other types of related information.

The U.S. Food and Drug Administration (FDA) Center for Food Safety and Applied Nutrition (CFSAN) has the mandate to assure the safety of the U.S. food supply. To help accomplish this task, the Center has created a database that currently contains all oral toxicity information available on almost 1700 of approximately 3000 direct food additives regulated in the United States. This database is called the priority-based assessment of food additives (PAFA).

History of PAFA

The origin of PAFA can be traced to 1969 when, in the wake of questions concerning the artificial sweetener cyclamate, President Nixon asked that the toxicology of all gererally recognized as safe (GRAS) compounds be reviewed. The scope of the project was expanded in 1977 by former FDA Acting Commissioner Gardner, who ordered periodic reviews of all oral toxicology studies of GRAS compounds as well as direct food additives. These cyclic reviews were to result in the creation of listings of food additives in order of their priority for the requirement of further toxicological evaluation. The database resulting from these reviews was to be called the cyclic review of ingredient safety profiles (CRISP).

The mammoth task of compiling all the necessary information finally started in 1981 when toxicologists and consumer safety officers of the (then) FDA Bureau of Foods began to create extensive, evaluated, and abstracted toxicology safety profiles for hundreds of food additives. At about this same time, when CFSAN managers realized that the size of the task compared to the resources available would not allow for the regular periodicity of the reviews, the name of the database was changed to the current priority-based assessment of food additives. However, as indicated by this name, the ability to compare the safety of different food additives was retained. During this same time, the electronic storage of PAFA began, using the resources of mainframe computers at the Federal government's Parklawn Computer Center in Rockville, Maryland, and the Model 204 database programming language.

Upon further realization of the resources this task demanded, in 1987 an outside contract was awarded for reviewing, updating, and further expanding the PAFA database. This contract was renewed in 1990 for continuing the updating of PAFA as well as enlarging the database to include all genetic toxicology studies of substances previously reviewed and all toxicity data for the remaining 1300 (mostly GRAS) compounds, which up to this time could not be included.

Another major event came in 1989 when the computer software used to access PAFA was reorganized and simplified, and

*U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Division of Toxicological Review and Evaluation, HFF-156, Washington, DC 20204.

Address reprint requests to R. D. Benz, U. S. Food and Drug Administration, Center for Food Safety and Applied Nutrition, Division of Toxicological Review and Evaluation, HFF-156, 200 C Street, S.W., Washington, DC 20204.

additional data fields were added. This improvement is now leading to the next major milestone, when in 1991 the PAFA database will be made available to the general public via direct on-line access through accounts with the U.S. National Technical Information Service, the database searching capability of the National Library of Medicine, and through general publication on compact disk (CD).

Other plans for the near future include entering all PAFA genotoxicity data into the U.S. Environmental Protection Agency Genetic Activity Profiles (GAP) database and modifying the software that is used to operate GAP to display in similar format the general toxicological data in PAFA.

Information in PAFA

The PAFA project involves many people from different divisions in FDA/CFSAN and the contract group engaged in continually updating and maintaining the database. Administrative and chemical information concerning the compounds in PAFA is reviewed regularly. For example, the poundage of each direct food additive annually used in the U.S food supply is monitored periodically through contracts with the U.S. National Academy of Sciences. In general, to make the most efficient use of limited resources, the greater the amount of the chemical that is used, the more frequently the toxicology information is updated: All oral and genetic toxicity data for food additives used at levels exceeding 1000 pounds (460 kg) each year are updated at least annually; the toxicology data on chemicals that are not currently being used at all are not updated.

Paper copies of all primary data collected for the PAFA database and their written reviews and evaluations are kept at CFSAN in a consistent format in hard-copy "food additive safety profile" (FASP) folders for each individual compound or group of compounds. All information is independently checked twice for accuracy; then most of it is also stored in the computer database. The Center has developed computer programs to access this information and to rank the compounds in order of concern to determine those chemicals that need additional attention and the toxicological consequences of substituting one food additive for another. The criteria for choosing the toxicological evaluation and ranking were first published by FDA/Bureau of Foods in 1982 in *Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food* (*1*), commonly referred to as "the Redbook."

PAFA's primary function is to serve as CFSAN's institutional memory for the toxicological effects of direct food additives. The database is also routinely used by CFSAN managers and review scientists to help evaluate the overall safety of the additives that have been reviewed and entered in a standard abstracted format in the PAFA database, to find compounds with certain defined toxicological effects, and to rank compounds for their relative toxicity in comparison to other food additives. PAFA is also used by CFSAN consumer safety officers as an easily accessible and consistent source of information to answer outside inquiries, by CFSAN laboratory scientists for background information for research they are doing or planning, and by various CFSAN professionals as a source of information for publications (e.g., *2–5*).

PAFA is composed of an umbrella file called EAFUS (everything added to food in the United States) containing all compounds known to be added to food in the U.S. food supply, including direct, secondary direct, and GRAS compounds. PAFA does not contain substances that are indirect food additives, food contaminants, or natural food constituents, but their future inclusion is desirable. All compounds in the database have at least a minimum assemblage of information, including the Chemical Abstract Services (CAS) Registry numbers, the U.S. Code of Federal Regulations (CFR) citation numbers, and the best estimate of the U.S. population exposure (if available). Well over half the compounds have complete, up-to-date toxicological information as well. As of May 2, 1991, toxicological information was available on 1685 regulated direct food additives and minimal information was available on 1236 additional additives for a total of 2921 substances in PAFA.

PAFA contains up to 180 different kinds of information (fields) about each chemical. Administrative and chemical information includes CAS numbers, the places where the chemicals are listed in the *U.S. Code of Federal Regulations*, the pounds disappearing into the U.S. food supply annually, the estimated daily human consumption (milligram per kilogram body weight per day) for each chemical, the Joint Expert Committee on Food Additives (JECFA) allowable daily intakes, the Redbook structure categories of the chemicals, and their technical effects.

Toxicology information includes the type of studies done for each chemical, the species of animals tested, the toxicological effects observed and the sites where they were seen, the lowest doses to cause a toxicological effect in each study, a literature citation for the studies if published or a CFSAN Document Control Center reference if reports are unpublished, and other types of related information.

Specific Structure and Contents of PAFA

To aid in searches of the database, PAFA's electronic storage is divided into two major types of records: administrative/chemical (RECTYPE=1) and toxicological (RECTYPE=2). These are then further subdivided into smaller sections called BOXes. Although RECTYPE=1 and BOX=1 are synonymous, RECTYPE=2 is divided into eight BOXes. BOX=3 contains the genotoxicity data, BOX=7 holds acute oral toxicity information, and BOX=9 (currently containing the vast majority of the studies in the database) has all oral toxicity data other than acute studies.

The information in the other five BOXes in RECTYPE=2 are derived from that in BOX=9 to facilitate access. BOX=4A contains the data from the one reliable study in BOX=9 that demonstrates the lowest effect level (LEL) in a mouse or rat for the compound of interest; similarly, BOX=4B highlights the data from that one study in BOX=9 that demonstrates the LEL in dogs for the compound of interest, and BOX=4C shows the LEL in any species for the compound in question.

BOX=6, on the other hand, holds the data from a study in BOX=9 that shows the highest no-effect level of the chemical in the same species as listed in BOX=4C. Finally, BOX=8 groups, for emphasis, those studies in BOX=9 that demonstate toxicological effects of high concern such as hyperplasia, teratogenicity, etc. The specific fields in the database are listed and defined in detail in the Appendix.

PAFA continues to be a highly valued resource of FDA/CFSAN. We are looking forward to making it available universally so that it may become a valued resource for all persons interested in the safety of food additives.

Appendix

Fields in PAFA

RECTYPE=1: RECTYPE=1 includes information such as structure, exposure, minimum testing level, and identification numbers.

BOX=1 Fieldnames: Chemistry and Administrative Information: BOX=1 is the only subdivision of RECTYPE=1.

BFD.GROUP*	Number of the Flavors and Extracts Manufacturers Association (FEMA) monograph that deals with the chemical.
BOX	BOX number on the Effect Summary Form (ESF).
CAS	Chemical Abstract Service (CAS) Registry numbers for the chemical. This is the record key.
CHEMFNTN‡	How the chemical is regulated: C=color; D=direct food additive; F=flavor; G=GRAS compound; I=indirect food additive; P=prior sanctioned.
COMMENTS	Additional information.
DENSITY	Density of the chemical.
DOCNUM	PAFA food additive safety profile (FASP) folder number for the chemical or "everything added to food in the United States" (EAFUS) number.
DOCTYPE	Type of document in PAFA covering the chemical: ASP=up-to-date food additive safety profile available covering administrative, chemical, and toxicological information; BAN=compound was banned and removed from the PAFA database but some nonupdated hardcopy data may be available; EAF=everything added to food in the U.S.: only limited administrative and chemical information available; NEW=compounds that have been selected for addition to PAFA will be labeled NEW until the safety profile has been completed and then will be renamed DOCTYPE=ASP; NIL=data may not be updated because exposure reported to be 0; or OLD=compound has been removed from the PAFA database but some nonupdated hardcopy data may be available. It is no longer regulated and is no longer GRAS.
EUROPE*	European Economic Community identification number for the chemical.
EXPOSURE	Population exposure to the chemical, i.e., the pounds disappearing into the U.S. food suppy annually. Derived from a NAS survey (see below) or FDA's estimate.
EXPOSURE.82	Pounds reported by the National Academy of Sciences (NAS) 1982 survey to be disappearing into the U.S. marketplace (corrected assuming 60% reporting).
EXPOSURE.87	Pounds reported by the NAS 1987 survey to be disappearing into the U.S. marketplace (corrected assuming 60% reporting).
EXPSRC	Last two digits of the year of the NAS exposure poundage information appearing in the EXPOSURE field or other source of this information.
FEMA	Identification number assigned by Flavors and Extracts Manufacturers Association for the chemical.
FUCODE	Y=chemical might be used in beverages; or N=chemical is not used in beverages.
FW	Formula weight of the chemical.
GRAS	Number of the FEMA expert panel paper that lists the chemical.
H.C.	Human consumption of the chemical (milligram/kilogram body weight/day per capita) assuming only 10% of the U.S. population consumes the entire annual EXPOSURE amount.
JECFA	Status of the chemical before the WHO/FAO Joint Expert Committee on Food Additives (JECFA): FU=full or unconditional acceptable daily intake (ADI); LGMP=ADI limited by Good Manufacturing Practice; NO=ADI not allocated; NS/NL=ADI not specified/limited; or TE=temporary ADI. (Codes FU-C and TE-C are used to indicate that the ADI applies to the entire class of which the chemical is a member.)
JECRA.ADI	Acceptable daily intake of the chemical set by JECFA. (milligram/kilogram body weight/day).
JECFA.YEAR	Last two digits of the year in which JECFA last reviewed the chemical.
LIT.UPDATE	Date of last literature search for the chemical (year-month-day).
LOGP	Octanol/water partition coefficient of the chemical.
MAINTERM	Preferred FDA/CFSAN chemical name.
MTL	Minimum testing level required for the chemical: 1, 2 or 3, as defined by the Redbook.
MX‡	Chemical components of the mainterm chemical.
MXCAS	CAS numbers of the components of the mainterm chemical.
NAR	Highest quality (A) tests not yet available but recommended for a full safety profile of the chemical.
NAS	National Academy of Sciences identification number for the chemical.
NATURE*	Chemical type as designated by FEMA: 1=natural flavor isolated by physical methods; 2=flavor identical to a natural flavor from aromatic raw materials or synthesized materials; or 3=artificially synthesized flavor.
PERSON*	Consumer safety officer or toxicologist who has prepared this information.
REGNUM	Regulation numbers in Title 21 of the *Code of Federal Regulations* where the chemical is listed.
SORTTERM	Preferred chemical name with all numbers, punctuation, etc., removed to facilitate sorting.
STR.CLAS	Broad chemical structure class of the chemical: A, B, or C assigned according to Appendix 1 of the Redbook.
STR.RULE	Specific chemical structure rule: 1, 2, 3, etc., assigned according to Appendix 1 of the Redbook.
STRUCTUR	Chemical structure categories of the functional groups of the chemical assigned according to Appendix 1 of the Redbook.
SURVEY	Phase number of the NAS/NRC survey covering the intake of the chemical.
TECH.EFF‡	The purpose for which the chemical is used as a food additive.
UK*	United Kingdom designation of the chemical type: 1, 2, or 3 for natural substances or 5 or 6 for synthetic substances.
UPDATE	Date of the latest update of the record for the chemical (year-month-day).

RECTYPE=2: RECTYPE=2 contains all pertinent toxicological information. For an explanation of the ranking of compounds, consult the Redbook (*1*).

Box=3 Fieldnames: Genetic Toxicology Information: BOX=3 contains a summary of all genetic toxicology reports available for the chemical of interest. There is one record for each genetic toxicology study reviewed.

BOX	BOX number on the Effect Summary Form (ESP).
CAS	Chemical Abstract Service (CAS) Registry number for the chemical. This is the record key.
COMMENTS‡	Additional information concerning toxicologic effects.
DOCNUM	PAFA FASP folder number for the chemical or EAFUS identification number (same as in BOX=1).
DURATION‡	Duration of the exposure (hours).
EFFECT‡	Toxicologic effects observed.
HNEL‡	Highest dose (milligram/kilogram body weight/day or milligram/milliliter) that did not cause a toxicologic effect.
LEL‡	Lowest dose (milligram/kilogram body weight/day or milligram/milliliter) that caused a toxicologic effect.
QUALITY‡	Quality of study by Redbook criteria: A=meets current standards; B=meets core standards; or C=does not meet current standards.
SITE‡	Strain or cell type used for study.
SOURCE‡	Source of toxicology information (literature or other reference).
STUDY	FASP data inventory catalog number for the study.
SUBJECT‡	Organism observed for effect.
TOPIC‡	Test type (end point).

*Data in these fields may not have been updated recently.
‡Data in these fields are currently being entered and may not be complete.
‡‡There are no data in these fields at this time.

UPDATE	Date of the latest update of this record (year-month-day).
Year‡	Last two digits of the year study was conducted or published.

BOX=4 Fieldnames: Lowest Effect Level Observed in All Available Rat or Mouse Studies (Box=4A), Dog (Box=4B), or All (Box=4C) Studies: BOX=4A highlights the lowest effect level (LEL) observed for the compound in all rat or mouse studies available in BOX=9. BOX=4B highlights the LEL observed for the compound in all available dog studies. BOX=4C highlights the LEL observed for the compound in all available studies of any species. In most cases the information in BOX=4C is a repetition of BOX=4A or BOX=4B. The effects in all BOXes=4 have been shown to be reproducible and are taken from studies with the longest duration and best quality where possible. Note: Results from reproduction or teratology studies are usually excluded from BOXes=4 because these studies do not reflect exposure to all of the general population.

BOX	BOX number on the Effect Summary Form (ESF).
CAS	Chemical Abstract Service (CAS) Registry number for the chemical. This is the record key.
COMMENTS	Additional information concerning toxicologic effects.
DOCNUM	PAFA FASP folder number for the chemical or EAFUS identification number (same as in BOX=1).
EFFECT	Toxicologic effects observed.
LEL	Lowest dose (milligram/kilogram body weight/day that caused a toxicologic effect.
QUALITY	Quality of study by Redbook criteria: A=meets current standards; B=meets core standards; or C=does not meet at least core standards.
R	Ranking factor: the human consumption (H.C.) divided by the LEL.
SITE	Organs or tissues where the effects were observed.
STUDY	FASP data inventory catalog number for the study.
SUBJECT	Species used for toxicologic testing.
UPDATE	Date of the latest update of this record (year-month-day).

BOX=6 Fieldnames: Highest Observed No-Effect Level in Same Species as BOX=4C: Box=6 highlights the highest observed no-effect level (HNEL) found among studies in BOX=9 for the same species as listed in BOX=4C. Quality=C studies are not used for this BOX.

BOX	BOX number on the Effect Summary Form (ESF).
CAS	Chemical Abstract Service (CAS) Registry number for the chemical. This is the record key.
COMMENTS	Additional information concerning toxicologic effects.
DOCNUM	PAFA FASP folder number for the chemical or EAFUS identification number (same as in BOX=1).
EFFECT	Toxicologic effects observed.
HNEL	Highest dose (milligram/kilogram body weight/day) in QUALITY=A or B studies that did not cause a toxic effect.
LEL	Lowest dose (milligram/kilogram body weight/day) that caused a toxicologic effect in the study from which the HNEL is derived.
QUALITY	Quality of study by Redbook criteria: A=meets current standards or B=meets core standards.
SITE	Organs or tissues where the effects were observed.
STUDY	FASP data inventory catalog number for the study.
SUBJECT	Species used for toxicologic testing.
UPDATE	Date of the latest update of this record (year-month-day).

BOX=7 Fieldnames: Acute Toxicology Information: BOX=7 contains a summary of all oral acute toxicology reports available for the chemical of interest. There is one record per species for which there are studies.

BOX	BOX number on the Effect Summary Form (ESF).
CAS	Chemical Abstract Service (CAS) Registry number for the chemical. This is the record key.
COMMENTS	Additional information concerning toxicologic effects.
DOCNUM	PAFA FASP folder number for the chemical or EAFUS identification number (same as in BOX=1).
EFFECT‡‡	Toxicologic effects observed.
LD50.HIGH	Dose (milligram/kilogram body weight) calculated to cause death in 50% of animals tested.
SITE‡‡	Organs or tissues where the effects were observed.
SOURCE‡	Source of toxicology information (published literature or other reference such as contained in the USFDA/CFSAN Document Control Center).
STUDY	FASP data inventory catalog number for the study.
SUBJECT	Species used for toxicologic testing.
UPDATE	Date of the latest update of this record (year-month-day).
YEAR‡	Last two digits of the year study was conducted (unpublished data) or published (open literature citation).

BOX=8 Fieldnames: High Concern Effects: BOX=8 highlights effects of high concern found in BOX=9 (i.e., proliferative, necrotic, reproductive, developmental and teratological effects). The LEL and HNEL for the effect may be from different studies if an HNEL can be found from a longer duration or better quality study.

BOX	BOX number on the Effect Summary Form (ESF).
CAS	Chemical Abstract Service (CAS) Registry number for the chemical. This is the record key.
COMMENTS	Additional information concerning toxicologic effects.
DOCNUM	PAFA FASP folder number for the chemical or EAFUS identification number (same as in BOX=1).
EFFECT	Toxicologic effects observed.
HNEL	Highest dose (milligram/kilogram body weight/day) that did not cause a toxicologic effect.
HNEL.QUAL	Quality of HNEL study by Redbook criteria: A=meets current standards; B=meets core standards; or C=does not meet at least core standards.
HNEL.STUDY	FASP data inventory catalog number for the HNEL study.
LEL	Lowest dose (milligram/kilogram body weight/day) that caused a toxicologic effect.
LEL.QUAL	Quality of LEL study by Redbook criteria: A=meets current standards; B=meets core standards; or C=does not meet at least core standards.
LEL.STUDY	FASP data inventory catalog number for the LEL study.
R	Ranking factor: the human consumption (H. C.) divided by the LEL.
SITE	Organs or tissues where the effects were observed.
SUBJECT	Species used for toxicologic testing.
UPDATE	Date of the latest update of this record (year-month-date).

BOX=9 Fieldnames: Oral Toxicology Information: BOX=9 contains a summary of all oral toxicology reports (other than acute) available for the chemical of interest. There is one record per species tested for each toxicology study reviewed.

BOX	BOX number on the Effect Summary Form (ESF).
CAS	Chemical Abstract Service (CAS) Registry number for the chemical. The is the record key.
COMMENTS	Additional information concerning toxicologic effects.
DOCNUM	PAFA FASP folder number for the chemical or EAFUS identification number (same as in BOX©1).
DURATION	Duration of study (days).
EFFECT	Toxicologic effects observed.
HNEL	Highest dose (milligram/kilogram body weight/day) that did not cause a toxicologic effect.
LEL	Lowest dose (milligram/kilogram body weight/day) that caused a toxicologic effect.
QUALITY	Quality of study by Redbook criteria: A=meets current standards; B=meets core standards; C=does not meet at least core standards.
SITE	Organs or tissues where the effects were observed
SOURCE‡	Source of toxicology information (published literature or other reference such as contained in the USFDA/CFSAN Document Control Center).
STUDY	FASP data inventory catalog number for the study.
SUBJECT	Species used for toxicologic testing.
TOPIC	Type of toxicity test done.
UPDATE	Date of the latest update of this record (year-month-day).
YEAR	Last two digits of the year study was conducted or published.

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