



HARNESSING CAS STNEXT[®] FOR REGULATORY SEARCHES

Sources and best practices

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Regulatory searches

Agenda

- What is a regulatory search and why is it needed?
- Different agencies, regulations, and requirements
- Leveraging CAS STNNext for regulatory searches
 - Sources of regulatory information
 - Databases
 - Strategy
- Example

What is a regulatory search?

Why is it needed?

A regulatory search is required

- To follow the regulatory guidance from a specific regulatory agency
 - Regulations differ among jurisdictions
- To assess environmental or toxicological safety of a chemical/pharmaceutical substance

Why is a substance regulated?

- A regulated substance is any substance which pursuant to environmental law is identified as hazardous or is identified to be subjected to special requirements.
- Requirements related to:
 - Use
 - Storage
 - Transportation
 - Disposition or handling



WHICH TYPE OF SUBSTANCES?

Pesticides or biocides

Food or food additives

Active ingredients of a product

When is a regulatory search needed?

How is it conducted?

Reasons to conduct a regulatory search:

- Product development
- (Re-)registration according to different operation procedures and international guidance

Products/active agents/ingredients searched in combination with:

- Properties like performance, safety, oral exposure, allergenicity, persistence, bioaccumulation
- Specific regulatory profiles (analytical methods, physical/chemical properties, toxicology, ecotoxicology, environmental fate, and residues)

European regulatory agencies

Regulations and requirements

- EFSA – European Food and Safety Authority

EU agency that provides independent scientific advice and communicates emergency risks associated with the food chain

- ECHA – European Chemicals Agency

Manages the technical and administrative implementation of REACH regulation.

- REACH – Registration, Evaluation, Authorisation and Restriction of Chemicals

- National authorities may have additional requirements

US federal regulatory agency

Regulations and requirements

- FDA – Food and Drug Administration
- belongs to the US Department of Health and Human Services.

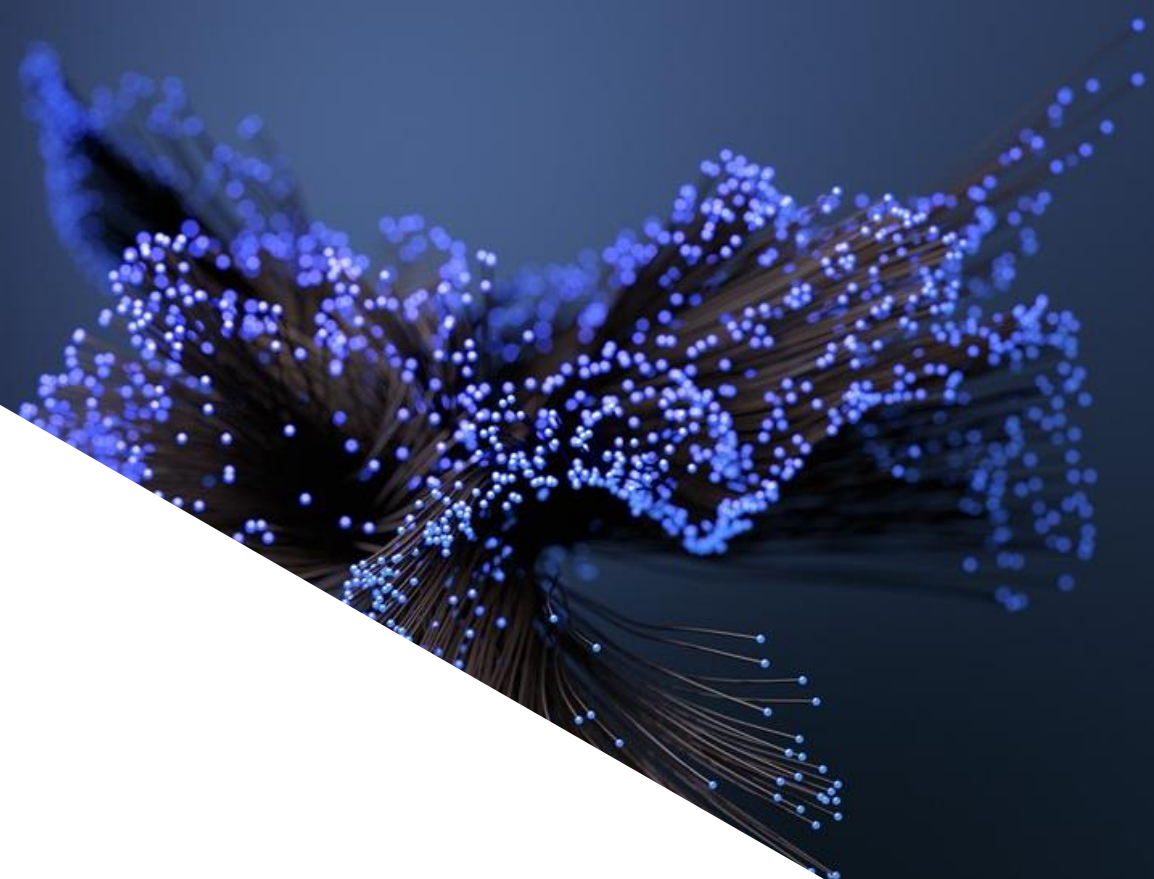
Responsibilities:

Protecting and promoting public health by controlling and supervising food safety, dietary supplements, prescription and over-the-counter drugs, medical devices, animal foods and feed etc...



SOURCES OF REGULATORY INFORMATION

Substance databases
Bibliographic databases



Sources for regulatory searches (1)

CAS STNext substance databases

– CAS REGISTRY®

- The most authoritative collection of disclosed chemical substance information
- Unique CAS RN for each substance record
- 1800s to present, updated daily

– RTECS

- **Registry of Toxic Effects of Chemical Substances**
- 1971 to present, updated quarterly

– CHEMLIST

- Regulated chemicals information
- 1979 to present, updated weekly
- covers multiple inventories
 - national inventories
 - USA and state regulations
 - international regulations
 - REACH substance list

Sources for regulatory searches (2)

International and National sources in CHEMLIST

European Union

- European Inventory of Existing Commercial Chemical Substances and EINECS Corrections (English) (March 1997)
- European List of Notified Chemical Substances
- List of Pre-Registered Substances for REACH
- List of Registered Substances
- REACH: Annex XVII: Dangerous Substances and Preparations
- REACH: Annex XIV: Substances Subject to Authorisation
- REACH: Candidate list of Substance of Very High Concern (SVHC) for Authorisation

=> HELP LISTS

Sources for regulatory searches (3)

CAS STNext bibliographic databases

Leaving no stone unturned

Aim for the most comprehensive coverage possible, harnessing the different relevant databases which are accessible in STNext

- MEDLINE, TOXCENTER, CAPLUS^(SM), GEOREF, AGRICOLA, CABA, FSTA, BIOSIS, PQSCITECH, ESBIODBASE, EMBASE, ANABSTR and SCISEARCH
- Toxicology information and information related to food science
- Dependent on the scope of the search
- Additional databases, e.g., CIN (Chemical Industry Notes), ADISNEWS

CAS STNext for regulatory searches

Overview of some Bibliographic databases

- **CAPLUSSM** provides worldwide coverage of from all areas of chemistry and related scientific disciplines.
 - CAPLUS covers different types of documents comprising both patent and non-patent literature
 - Records are reference-based containing bibliographic data, abstracts and indexing information
 - Indexed with Registry Numbers (/RN) and role information (/RL)

CAS STNext for regulatory searches

Overview of some Bibliographic databases

- **EMBASE** (Excerpta Medica) covers the worldwide literature on **biomedical** and **pharmaceutical** fields.
 - Produced by Elsevier including, journal articles, books, conference proceedings and reports
- Records contain:
 - Bibliographic information
 - Drug trade names (/CN), their manufacturers (/CO), medical device trade names (/CN) and manufacturers (/CO)
 - CAS Registry Numbers
 - Controlled terms

CAS STNext for regulatory searches

Overview of some Bibliographic databases

- **Medline** (MEDlars onLINE) covers worldwide **biomedical** literature
 - Produced by the U.S. National Library of Medicine (NLM) comprising mainly journal articles
- Records contain:
 - Bibliographic information
 - CAS Registry Numbers
 - Chemical Name (/CN), Controlled Term (/CT), Medical Subject Headings - MeSH Tree Number (/MN)
Thesauri

CAS STNext for regulatory searches

Overview of some Bibliographic databases

- **BIOSIS Previews/RN[®]** covers worldwide research on all biological and biomedical topics
 - Produced by Clarivate Analytics
 - Covers journal articles, reports, reviews, books, conference articles, US patents
- Records contain bibliographic data, abstracts for most references and indexing information:
 - Records are indexed with chemical names (/CN) and Registry Numbers (in /BI) for substances
 - Concept Code (/CC), Controlled Term (/CT), Organism (/ORGN) and Geographic Term (/GT) thesauri

CAS STNext for regulatory searches

Overview of some Bibliographic databases

- **TOXCENTER** (Toxicology Center) is a bibliographic database covering pharmacological, biochemical, physiological and **toxicological effects** of drugs and other chemicals.
 - Includes references from CAPLUS, BIOSIS, MEDLINE, IPA and others

Records are reference-based containing bibliographic data, abstracts, indexing information:

- Linked to CAS Registry Numbers and chemical names for substances (/CN or /IT)
- File Segment (/FS)
- Includes MeSH Terms (/MN)

Database Summary Sheet

DISPLAY and PRINT Formats

Any combination of formats may be used to DISPLAY and PRINT answers. Multiple codes may be separated by spaces or commas, e.g., D RN FA. The fields are defined in the CHEMLIST/HCHEMLIST file. Highlighting is available in all fields except AN and FA. Highlighting codes are defined in the CHEMLIST/HCHEMLIST file.

Format	Content
4A (TES)	Test Rule - TSCA Section 4A
4E (ITC)	Interagency Testing Committee
4F (RIS)	Risk May Be Unreasonable
5A1 (PMN)	Premanufacture Notice
5A2 (RSNU)	Significant New Use Rule
5E (INS)	Insufficient Data Order
5H (EXM)	Exemption from PMN
8A (REP)	Report on Volume, Exposure, Etc.
8D (UNP)	Rule Calling for Unpublished Health/Safety Study
8E (SRR)	Substantial Risk Report
AAQS	Clean Air Act National Ambient Air Quality Standards
AN (1)	Accession Number
CANL	Canadian Legislation Affecting Chemicals
CBI	Confidentiality Status
CERHS	CERCLA Hazardous Substances
CFR	CFR Title
CGB	DOT Coast Guard Bulk Hazardous Materials
CGN	DOT Coast Guard Noxious Liquids
CHP	Chemical Hazard Information Profile
CLP (EECDs)	Classification, Labeling, and Packaging
CN (2)	Chemical Name
CWA	Clean Water Act Sections 301, 307, and 311
DEA	Drug Enforcement Administration Precursor
DEF	Definition for UVCB Substances
EECL	European Community Legislation
EHS	SARA Title III/EPCRA Extremely Hazardous Substances
FA (1)	Field Availability
FCN (3)	Full Chemical Name
FDA	Federal Drug Administration Regulations
FGRAS	FDA Food Substances Generally Recognized as Safe
FS	File Segment

CHEMLIST/HCHEMLIST

SEARCH and DISPLAY Field Codes

The field that allows left truncation (/BI) is marked with an asterisk (*).

Search Field Name	Search Code	Search Examples
Basic Index * (contains CAS Registry Numbers, single words from the CN, CFR, INV, INVT, SC, and UVC fields, EPA numbers, and summary text of each section of the law) (1)	None (or /BI)	S ?BROMO? AND INHAL? S 77-47-4 or S ECOTOXIC? S P 79-11
Accession Number	/AN	S 33063/AN
ACGIH Threshold Limit Values	/TLV	S BENZENE/TLV
California Proposition 65 List	/PROP65	S REPROD? TOXIC? /PROP65
Canadian Legislation Affecting Chemicals	/CANL	S IMPORT?/CANL
CAS Registry Number	/RN	S 77-47-4/RN
CERCLA Hazardous Substances	/CERHS	S RQ/CERHS
CFR Section	/SC	S 29 CFR 1910.119/SC
CFR Title (2)	/CFR	S 40 CFR PART 116/CFR
Chemical Hazard Information Profile	/CHP	S CARCIN?/CHP
Chemical Name	/CN	S M-CRESOL/CN
Chemical/Physical Properties	/PROP	S SOLUBILITY/PROP
Citizens' Petition - TSCA Section 21	/PET	S PCB/PET
Classification, Labeling, and Packaging	/CLP (/EECDs)	S ACETATE/CLP
Clean Air Act 1990 Amendments Hazardous Air Pollutants	/HAP	S ACETALDEHYDE/HAP
Clean Air Act National Ambient Air Quality Standards	/AAQS	S AEROSOL/AAQS
Clean Air Act Ozone Depleting Compounds	/ODC	S METHYL BROMIDE/ODC
Clean Air Act Section 111 Volatile Organic Compounds	/VOC	S EMISSION STANDARDS/VOC
Clean Water Act Sections 301, 307, and 311	/CWA	S POLLUTANT/CWA
Confidentiality Status	/CBI	S PUBLIC/CBI
Cross-Reference Registry Number	/XRN	S 9000-78-6/XRN
Definition for UVCB Substances	/DEF	S FATTY ACID#/DEF
DOT Coast Guard Bulk Hazardous Materials	/CGB	S BUTYROLACTONE/CGB
DOT Coast Guard Noxious Liquids	/CGN	S BUTYRIC ACID/CGN
DOT Hazardous Materials Table	/HAZT	S FORBIDDEN/HAZT
Drug Enforcement Administration Precursor	/DEA	S DESOMORPHINE/DEA

CHEMLIST® / HCHEMLIST (Regulated Chemicals Listing)

The two files differ only in pricing metrics.



Subject Coverage	<ul style="list-style-type: none"> Substance inventories Regulatory lists Dangerous chemicals 										
File Type	Directory, Substance, Inventory										
Features	<table border="0"> <tr> <td>Thesaurus</td> <td>Not available</td> </tr> <tr> <td>Alerts (SDIs)</td> <td>Weekly</td> </tr> <tr> <td>CAS Registry Number® Identifiers</td> <td><input checked="" type="checkbox"/> Page Images <input type="checkbox"/></td> </tr> <tr> <td>Keep & Share</td> <td><input checked="" type="checkbox"/> SLART <input checked="" type="checkbox"/></td> </tr> <tr> <td>Learning Database</td> <td><input type="checkbox"/> Structures <input type="checkbox"/></td> </tr> </table>	Thesaurus	Not available	Alerts (SDIs)	Weekly	CAS Registry Number® Identifiers	<input checked="" type="checkbox"/> Page Images <input type="checkbox"/>	Keep & Share	<input checked="" type="checkbox"/> SLART <input checked="" type="checkbox"/>	Learning Database	<input type="checkbox"/> Structures <input type="checkbox"/>
Thesaurus	Not available										
Alerts (SDIs)	Weekly										
CAS Registry Number® Identifiers	<input checked="" type="checkbox"/> Page Images <input type="checkbox"/>										
Keep & Share	<input checked="" type="checkbox"/> SLART <input checked="" type="checkbox"/>										
Learning Database	<input type="checkbox"/> Structures <input type="checkbox"/>										
Record Content	<ul style="list-style-type: none"> Substance identity information, inventory status, source of information, and summaries of regulatory activity, reports, and other compliance information CHEMLIST offers the convenience of identifying—in one place—the regulatory requirements for a specific substance from many of the world's most significant regulated substances lists 										
File Size	More than 406,500 records (01/24)										
Coverage	Inventories and regulatory listings, 1980-present										
Updates	<ul style="list-style-type: none"> Updated weekly with more than 50 additions to existing records or new substances PMN/NOC information appears in CHEMLIST within a week of when it is published in the Federal Register 										
Language	English										
Database Producer	Chemical Abstracts Service 2540 Olentangy River Road P.O. Box 3012										

CAS STNext for regulatory searches

General strategy

- Search for chemical name and synonyms (and/or CAS RN)
- Restrict with the different profiles key words in basic index
 - More precision and restrictions by document type
- Further optional refinements:
 - Language, time range
 - Controlled vocabulary
- Use different files to find relevant information and enhance comprehensiveness
- Combine answer sets and remove duplicates
- Review; relevance checking



EXAMPLE

LITERATURE SEARCH ON BETANIN AS SUPPORT FOR A REGISTRATION DOSSIER IN EUROPE

Example

Betanin

- **Betanin** is also known as Beetroot Red and is a red glycosidic food dye obtained from beets, known as E162

Used in food stuffs such as for coloring meats and bacon products.

- **Example**

A regulatory search is necessary as support for a registration dossier in Europe.

Example

Betanin

1st step – Building the substance profile

Collect synonyms and different spellings, CAS RN Numbers, E-numbers or other potentially relevant information.

How?

Internet searches, CAS Lexicon in STNnext, the substance entry in REGISTRY and also the CAS Common Chemistry platform.

The screenshot shows the CAS Lexicon search interface. At the top, there are tabs for 'History', 'Project', 'CAS Lexicon', and 'Databases'. A search bar contains the text 'Betanin' with a search icon. Below the search bar, there are links for 'Clear' and 'Collapse All'. A list of chemical classes is shown with checkboxes: Pyridines, Aromatic alcohols, Indoles, Aryl glycosides, Unsaturated compounds, Tricarboxylic acids, and Glucopyranosides. The 'Betanin' class is selected and highlighted in blue, with an 'Add All' button next to it. Below this, a 'Synonyms' section is expanded, showing a list of synonyms with checkboxes and 'Add All' buttons: Betanidin 5-β-D-glucopyranoside, Betanine, Phytolaccanin, NSC 170989, (15S)-Betanin, and B 0397. At the bottom of the search results, there is an 'OR' dropdown menu and an 'Add Term' button. Below the search results, there are icons for 'Draw' (with a 'NEW' badge) and 'Scripts'.

Example

Betanin

A simple and non-extensive Betanin profile could be:

que (Betanin# OR ph!tolaccanin# OR Betanidin 5-.beta.-D-glucop!ranoside OR “E162” or “E162” OR NSC170989 OR NSC 170989)

Variations of the searched term:

Betanin# → Betanine or Betanin (“#” 1 or 0 characters may be present)

ph!tolaccanin# → phytolaccanin# or phitolaccanin# (“!” 1 character must be present)

Beware of empty spaces in your keywords:

“E162” will retrieve a different number of results than “E 162”

The system handles “E 162” as “E(1w)162” which means that terms need to be adjacent in the specified order “E-162” is therefore also retrieved.

Example

Betainin – What about the CAS number?

Betainin CAS registry number is “7659-95-2” which can be incorporated in the keyword profile and also individually searched in the substance databases.

```
FILE 'REGISTRY' ENTERED AT 14:39:26 ON 15 MAY 2024
L1      1 SEA SPE=ON  ABB=ON  PLU=ON  7659-95-2/RN
        D

FILE 'HCAPLUS' ENTERED AT 14:39:50 ON 15 MAY 2024
L2      1779 SEA SPE=ON  ABB=ON  PLU=ON  L1
L3      2273 SEA SPE=ON  ABB=ON  PLU=ON  (BETANIN#/BI,BIEX OR PH!TOLACCANIN#
        /BI,BIEX OR BETANIDIN 5-B-D-GLUCOP!RANOSIDE/BI,BIEX  OR
        "E162"/BI,BIEX OR "E 162"/BI,BIEX OR NSC170989/BI,BIEX OR NSC
        170989/BI,BIEX)
L4      2422 SEA SPE=ON  ABB=ON  PLU=ON  L2 OR L3
```

The substance entry in REGISTRY corresponds to 1779 bibliographic references in CA.

Keyword profile - ca. 650 additional references are found.

Example

Betanin – What about the CAS number in CHEMLIST

L1 ANSWER 1 of 1 CHEMLIST COPYRIGHT 2024 ACS on STN
AN 111392 CHEMLIST
RN **7659-95-2**
INV On REACH
List of Pre-Registered Substances
<https://echa.europa.eu/substance-information/-/substanceinfo/100.028.753>.
On EINECS
Annex to Official Journal of the European Communities, 15 June 1990.
On AIIC
Australian Inventory of Industrial Chemicals
<https://industrialchemicals.gov.au>.
On TCSI
Taiwan Chemical Substance Inventory.
Listed Name(s): [S-(R*,R*)]-4-[2-[2-carboxy-5-(β-D-glucopyranosyloxy)-2,3-dihydro-6-hydroxy-1H-indol-1-yl]vinyl]-2,3-dihydropyridine-2,6-dicarboxylic acid
On NZIoC
New Zealand Inventory of Chemicals.
May be used as a component in a product covered by a group standard but it is not approved for use as a chemical in its own right.
On VNECI
Vietnam Draft National Chemical Inventory.

Inventories are easy to access:

=> S 7659-95-2/INV

Example

Betanin – Relevant keyword profiles

- 2nd step – Building the relevant keyword profiles

Creativity is needed

One of the profiles is “Allergenicity“ how to build it?

Possible Synonyms: Allergy, Allergen, sensitivity, elicitation, hypersensitivity etc

A simple and non-extensive search profile could be:

que (allerg? or sensit? or elicitat? or irritant or h!persensi? or h!per(w)sensi?)

Example

Betanin – Possible restrictions and optional refinements

- Only non-patent-literature is relevant
- A time restriction is usually necessary
- The document language can also be restricted in case of too many documents
- Start with the broadest possible query and narrow it down if necessary
- How many documents should be checked for relevance?

Example

Betanin – Possible restrictions and optional refinements

- Possible restrictions between Betanin and the Allergenicity profile.

Database/ Restriction	AND	5a	Ti,Ab
CA	193	44	81
MEDLINE	31	7	25
BIOSIS	29	7	28
EMBASE	32	8	25

Example

Betanin – Possible restrictions and optional refinements

- Controlled terms /CT
- CAPLUS:
 - Substance roles, Classification codes
- MEDLINE, EMBASE
 - Qualifiers/Link Terms, Limit Terms
- BIOSIS:
 - Classification/Concept codes, Limit Terms, Organism thesaurus
- TOXCENTER:
 - Classification codes, Qualifiers, Limit Terms, Organism thesaurus

MEDLINE → Substance (L) Major term
EMBASE → Substance (P) Major term

Example

Betanin – Possible restrictions and optional refinements

– CAS Roles

– Roles describe the new information reported about a substance in CAPLUS documents

– ADV adverse effect, including toxicity

– COS/DGN cosmetic/diagnostic use

– DMA drug mechanism of action

– PAC pharmacological activity

– PKT pharmacokinetics

– BCP biochemical process

=> S 7659-95-2/ADV
(7659-95-2 (L) ADV/RL)

At the command prompt => type HELP ROLES for more information

Example

Betanin – Which databases to use?

- Regulatory searches should be the most comprehensive possible.
- Possible databases:
MEDLINE, TOXCENTER, CAPLUS, GEOREF, AGRICOLA, CABA, FSTA, BIOSIS, PQSCITECH, ESBIODATABASE, EMBASE, ANABSTR and SCISEARCH
- Search strategy should be replicated;
- Wildcards might not be equally accepted;
- Broader or narrower strategies might be needed.

Example

Betanin – How to handle duplicates?

- The DUPLICATE REMOVE command will merge the different answers sets and remove duplicates.
- The merged set of unique answers is placed in an L-number answer set.
- Number of duplicates removed from the merged answer set are displayed.
- Answers are arranged by database and in reverse chronological order (newest to oldest).

Example of betanin and allergenicity in three different databases

```
L8          226 DUP REM L5 L6 L7 (42 DUPLICATES REMOVED)
           ANSWERS '1-205' FROM FILE HCAPLUS
           ANSWERS '206-216' FROM FILE MEDLINE
           ANSWERS '217-226' FROM FILE EMBASE
```


Example

Betanin – What about the relevance check?

- Typical a high amount of results must be checked for relevance
- What information is needed to perform this task?

```
L3 ANSWER 2 OF 157 HCAPLUS COPYRIGHT 2024 ACS on STN
TI Betanin dye extracted from ayrampo (Opuntia soehrensii) seeds to develop
dye-sensitized solar cells

L3 ANSWER 5 OF 157 HCAPLUS COPYRIGHT 2024 ACS on STN
TI Betanin from beetroot (Beta vulgaris L.) regulates lipid metabolism and
promotes fat browning in 3T3-L1 adipocytes
```

- After the relevance check results can be displayed in the desired format.

Summary

- Identify the regulatory agencies requirements
- Identify the databases which most likely provide suitable answers
- Build the necessary search profiles and strategy for the different databases
- Be critical of the displays that might be needed before and after the relevance check

Thank you

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Between problems and progress are connections that matter



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