IUCLID: A Database on Chemical Substances Information as a Tool for the EU-Risk-Assessment Program

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A database on so-called "Existing Chemicals" is being developed at the European Chemicals Bureau (ECB). The database IUCLID contains all data sets submitted by Industry following Council Regulation (EEC) 793/93[1] on the "Evaluation and Control of the Risks of Existing Substances". The Regulation obliges Industry to submit all readily available data on "High Production Volume Chemicals", using the HEDSET software package, to the ECB. Copies of the database are being used by the European Commission and in the EU-Member States Authorities as the data source for selecting priority substances and for carrying out the risk assessment on them. The outcome of the risk assessment process will be a validated IUCLID data sheet which includes a summary risk assessment report for each priority substance. The multilingual database is available from the ECB, in IUCLID format or as an easy to use CD-ROM version, including the original data submitted by Industry and later the validated data and the risk assessment reports.

INTRODUCTION

With the adoption of the sixth amendment to Council Directive 67/548/EEC[2] on September 18, 1979 (Council Directive 79/831/EEC[3] a distinction was made between "New" and "Existing" Chemicals. "Existing Chemicals" are those substances which were deemed to be on the European Market before September 18, 1981 and are listed in **EINECS**[4,5] (**E**uropean **In**ventory of **E**xisting **C**ommercial chemical **S**ubstances). This list contains in total 100 106 substances. All substances which have been placed on the market after September 18, 1981 are called "New Chemicals" and must be notified following the notification scheme introduced in the sixth amendment to the "Dangerous Substances Directive" 67/548/EEC. The seventh amendment to this Directive, Council Directive 92/32/EEC,[6] adopted on April 30, 1992, now requires that a risk assessment has to be carried out for these New Chemicals.

In order to set up a similar system for the evaluation of Existing Chemicals the EU-Member States adopted Council Regulation (EEC) 793/93 on the "Evaluation and control of the risks of existing substances" [1] on March 23, 1993 which came into force on June 4, 1993. The aim of the Regulation is to set up a frame within which it is possible to make a systematic assessment of the risks to man and the environment of the Existing Chemicals which are currently present on the European Market. The Regulation stipulates that the evaluation must follow three steps: a data collection step, a priority setting step, and a risk assessment step.

The data collection step is split into three phases. Initially, 1884 substances were extracted from the list of 100 106 Existing Chemicals which were expected to be produced in or imported to the European Union with a tonnage exceeding 1000 tonnes/year per producer or importer. This list was referred to as the list of **H**igh **P**roduction **V**olume **C**hemicals (**HPVC**s). These substances are listed in Annex I of Regulation (EEC) 793/93.

Producers and importers were obliged to submit a data set for each of these substances to the European Chemicals Bureau by June 4, 1994. During the second phase of data collection Industry had to report the substances with a production volume of more than 1000 tonnes/year, which are not listed in Annex I of the Regulation, by June 4, 1995. The total list of substances reported under phases 1 and 2 of the Regulation is now referred to as the EU-HPVC list. The third phase requires the submission of data for substances produced in the range of 10 to 1000 tonnes/year by June 4, 1998.

For the data collection a special computer program was developed by the European Commission, the HEDSET software package (**H**armonized **E**lectronic **D**ata **SET**). Industry must use the software for the compilation of the data sets which they submit under the Regulation. It has been designed to run on standard PCs and is available in 9 of the official EU-languages. It is mainly glossary driven, which makes it possible to define a specific structure and to allow an automated translation from one language to another.

The data is sent on a diskette to the Security Office of the Joint Research Centre in Ispra and then forwarded to the **ECB** (**E**uropean **C**hemicals **B**ureau) for data processing and storage. Here all export files are loaded onto the database **IUCLID**, the **I**nternational **U**niform **C**hemica**L** **I**nformation **D**atabase. The IUCLID database management software was developed parallel with HEDSET by the European Commission. This database is the basic tool for the priority setting and risk assessment steps under the Regulation. In order to achieve transparency in the priority setting step and disseminate the data for the risk assessment step, the IUCLID database has been installed within the Competent Authorities (CAs) in the EU-Member States.

The next step in the evaluation process is the priority setting step. The aim of this step is to select, among the HPVCs appearing in IUCLID, substances which need an in-depth investigation. The selection of substances is carried out in two stages: an automated stage and an expert judgement stage. An automated priority setting methodology, the so-called "IPS Method",[7] which has been agreed with the Competent Authorities of the Member States and with Industry, has been developed and translated into a

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Table 1. IUCLID Data Chapters and Subchapters Producer Related Part (Chapter 1)

chapter	chapter description
1	general information
1.1[a]	general substance information
1.2	synonyms
1.3[a]	impurities
1.4[a]	additives
1.5[a]	quantity
1.6.1[a]	labeling
1.6.2[a]	classification
1.7[a]	use pattern
1.8	occupational exposure limit values
1.9[a]	source of exposure
1.10	water pollution
1.11	major accident hazards
1.12	air pollution
1.13[a]	additional remarks

[a] These subchapters are regarded partly as confidential (see below).

computer program. The program creates, using certain endpoints on environmental and human health effects as well as certain exposure parameters which are stored in the IUCLID data sets, a ranking of the IUCLID substances, ordered by the degree of "concern". The ranking and the data used for the ranking is then commented on and adjusted by both, the CAs in the Member States and Industry during the expert judgment stage. The adjusted ranking forms the basis of a draft of a Commission proposal for a priority list. This draft is discussed at expert meetings with the CAs and Industry. Each priority substance is assigned to a Member State Authority, who is then given responsibility to carry out a risk assessment, following Commission Regulation (EEC) 1488/94[8] and using the guidance given in the "Technical Guidance Document for Risk Assessment".[9] The summary risk assessment report created by the "rapporteur" of the Member State Authority and the validated data sheet is included into IUCLID.

HEDSET

The first step in the Risk Assessment process is the data collection. The goal of the development of the HEDSET software was (1) to make the data collection as efficient as possible using little or no paper, (2) to provide an easy to use data-entry-screen system which allows for entering the required data, and (3) to have the software program run on a standard PC, available even in smaller companies. The HEDSET software presents a choice, e.g., test species or test methods, from a list of values, appearing in the appropriate language. An explanatory note accompanies the software as a guide on how to compile the data. After having completed the data set the export function creates an export-file in the HEDSET/IUCLID data exchange format. This file can be imported into other HEDSET or IUCLID installations for data exchange.

The HEDSET software is currently available in nine of the official EU-languages (Versions translated into Swedish, Finnish, and Norwegian are in preparation) and can be ordered free of charge from the ECB. Furthermore, the HEDSET Help-Desk assists the companies in case of technical problems or difficulties occurring by the installation or completion of the data sets.

Table 2. IUCLID Data Chapters and Subchapters Substance Related Part (Chapters 2−5)

chapter	chapter description
2	physicochemical data
2.1	melting point
2.2	boiling point
2.3	density
2.4	vapor pressure
2.5	partition coefficient
2.6	water solubility
2.7	flash point
2.8	auto flammability
2.9	flammability
2.10	explosive properties
2.11	oxidizing properties
2.12	additional remarks
3	environmental fate and pathways
3.1.1	photodegradation
3.1.2	stability in water
3.1.3	stability in soil
3.2	monitoring data (environment)
3.3.1	transport
3.3.2	distribution
3.4	mode of degradation in actual use
3.5	biodegradation
3.6	BOD5, COD, or BOD5/COD ratio
3.7	bioaccumulation
3.8	additional remarks
4	ecotoxicity
4.1	toxicity to fish
4.2	toxicity to aquatic invertebrates (e.g., daphnia)
4.3	toxicity to aquatic plants (e.g., algae)
4.4	toxicity to microorganisms (e.g., bacteria)
4.5.1	chronic toxicity to fish
4.5.2	chronic toxicity to aquatic invertebrates
4.6.1	toxicity to soil dwelling organisms
4.6.2	toxicity to plants
4.6.3	toxicity to other species
4.7	biological effects monitoring
4.8	biotransformation and kinetics
4.9	additional remarks
5	toxicity
5.1.1	acute oral toxicity
5.1.2	acute inhalation toxicity
5.1.3	acute dermal toxicity
5.1.4	acute toxicity, other routes
5.2.1	skin irritation
5.2.2	eye irritation
5.3	sensitization
5.4	repeated dose toxicity
5.5	genetic toxicity in vitro
5.6	genetic toxicity in vivo
5.7	carcinogenicity
5.8	toxicity to reproduction
5.9	developmental toxicity/teratogenicity
5.10	additional remarks
5.11	experience with human exposure
6	references
7	risk assessment

IUCLID

3.1. Purpose of IUCLID. In order to enable the European Commission, the Member States Authorities, Industry, and other organizations to handle the enormous amount of data collected under the Regulation, the European Commission had to develop a database system which would fulfil the following requirements:

(1) it should hold all data submitted by Industry;
(2) it should allow interface programs to query the database for specific properties in the standard SQL-Retrieval language;
(3) it should allow data exchange between several installations;

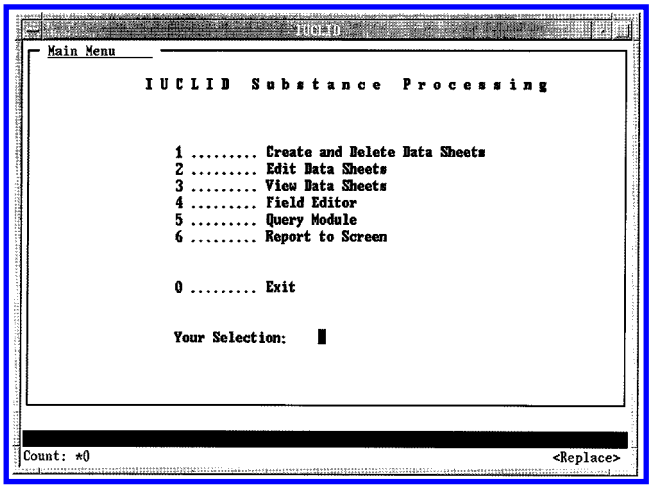

Figure 1. IUCLID main-module.

(4) it should be able to create reports on the substances;

(5) it should be able to run in different hardware environments under the most common operating systems.

3.2. IUCLID Design. The European Commission standard database management system Oracle was chosen as a suitable development platform.

The IUCLID structure and screens were designed to be fully compatible with the HEDSET forms. All glossary values have been coded instead of storing the actual text. This allows IUCLID and HEDSET to be multilingual and enables the user to select and change the language of the current IUCLID session on the same IUCLID installation. Furthermore, the glossary system allows a relatively easy translation of the system and the data into other languages at a later stage. The glossary system is important for the data exchange as well, as the export file has been designed to contain only the codes, which can then be translated into the appropriate language automatically. The IUCLID data base management software has been designed in several modules.

3.2.1. Main-Module. The main module is divided into six subitems: With "Create and Delete Data sheets" the user can define a new, empty data sheet for their own institution or company and then enter data. The creation date and the revision date can be edited.

With item "Edit Data sheet" the user may select a data sheet to be edited, e.g., by CAS-No., EINECS No. or combinations of CAS-No. and a specific company. The user may edit all the chapters of the own data sheet but can also merge data from several data sheets to the own data sheet. When entering or editing fields in the data sheets, the glossary key allows the user to select the desired entry from a list of values. If the desired entry, e.g., a test method which has been used, cannot be found, a so-called "other" key allows the entry of the data in the appropriate field. Freetext can be entered, e.g., to explain the specific test conditions or to give the references. Freetext entries are indicated by a freetext-type, such as "RM" for remark, "RE" for reference or "TC" for test-condition. Text can be imported into the free-text fields from ASCII-sources.

Records can be marked with flags for printing or export, which, e.g., contain reliability codes on the reported studies. The print or import/export function can then be restricted to these marked records. The print key starts the IUCLID report generator. Reports can be printed in the IUCLID standard layout or in a user-defined output format, the complete dossier or parts of it, by chapter or subchapter.

"View Data sheet" has the same functionality as the above, but database fields cannot be modified. Subqueries can be executed to extract specific tests from a series, e.g., to see all the results of all "Daphnia Tests" in chapter 4.2. Several data sheets from different companies can be shown together.

The "Field-Editor" is a tool to harmonize the occurrence of the same entries in the entire data sheet, if the entries are written using for example different spellings. This is, for example, a very useful tool to edit the references to remove double entries in the reference list.

"Query Module" calls the screen in which a search of the entire database can be performed. This module is explained in more detail in the next subsection.

"Report to Screen" shows the chapters as they would appear in the printout on the screen, with the freetext shown together with the test-results.

3.2.2. Query-Module. With the query-module searches for common properties or endpoints in the database can be performed. A predefined query can be selected. After having entered the query parameters the result can be shown on the screen or printed as a report. A new IUCLID installation already contains a set of predefined queries, e.g., search for EINECS entries by name fragments, CAS-Numbers or EINECS-Numbers. Complex queries for common properties, such as "show all log-P-values for substances taken from a list of CAS-Numbers, submitted by companies from a specific country" can be defined and executed by the user. These user-defined queries can be exchanged through a special query-export/import function creating ASCII files, which can be loaded into other IUCLID installations. An ftp-server for IUCLID queries has been set up at the ECB to allow the up- and downloading of IUCLID-Queries (Internet address: "ftp.ei.jrc.it", directory: /public/iuclid).

3.2.3. Administration-Module. With the IUCLID administration-module the system administrator can introduce new users and grant or restrict access permissions for, e.g., chapters which are regarded as confidential. This is important on distributed systems in larger companies. The previously mentioned queries for the query-module, the queries to retrieve data sheets, furthermore, general system definitions, layouts for reports, and printer settings are defined in the administration module.

3.2.4. Import/Export-Module. The import/export-module has been designed to exchange data sheets via the IUCLID data exchange format. The module creates export-files which can contain both single chapters as well as sets of complete data sheets. These files can be exchanged by diskette or, as long as the data are nonconfidential, even sent by e_mail or ftp via Internet.

3.3. Data Sheet Layout. For "New Substances" a well defined set of tests has to be carried out before a substance shall be placed on the market. For "Existing Substances" Industry must provide all relevant available data, but no further tests need to be carried out in the data collection step of the Regulation. An Expert Group, consisting of Commission Staff, National Experts, Experts from the OECD and

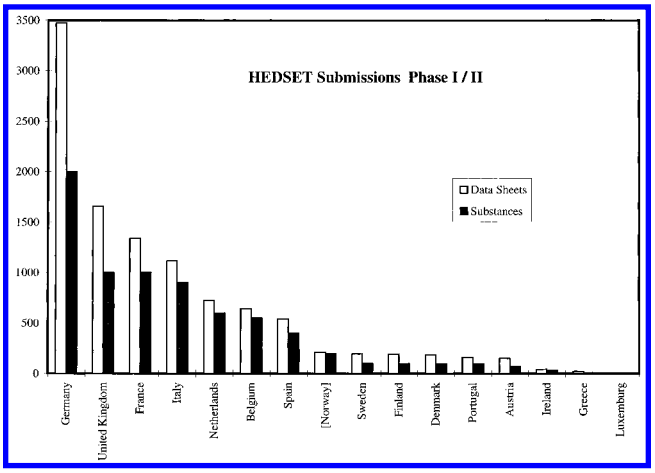

Figure 2. HEDSET submissions by European Industry.

Industry have defined the HEDSET/IUCLID data sheet for Existing Chemicals as follows.

Each data sheet consists of a **P**roducer **R**elated **P**art (**PRP**, Chapter 1) and a **S**ubstance **R**elated **P**art (**SRP**, Chapters 2−5). Each company, which originates a data sheet for a substance must complete the PRP. Several companies may reach an agreement that one company should be responsible for issuing the SRP. The other companies joining this consortium refer in their substance related in part to the responsible company. Chapter 6 is automatically generated for the references. Chapter 7 contains the summary risk assessment reports to be prepared by the rapporteurs after the substance has been evaluated.

A single data sheet in IUCLID is identified by the CAS-number, the company name, and the creation date. So one company may place different data sheets in IUCLID with the same CAS number but with a different creation date.

3.4. Statistics on the IUCLID Data. During phase I of the data collection the ECB had received by June 4, 1994, 7500 diskettes from Industry for 1400 different substances. By October 4, 1995, 10 750 data sheets are present in IUCLID for 2500 different substances. All in all 2400 companies have submitted data during the first two phases. Industry must submit updates of their data sheets if significant data or production figures change. Within phase III of the data collection step all substances listed in EINECS with a production range from 10−1000 tonnes/year must be reported. Data for more than 10 000 additional substances are expected to be loaded into IUCLID.

3.5. Data Quality. For all the information in chapters 2−5 in IUCLID the sources are given and also published. The submitting companies are responsible for the quality of the reported data. The Regulation stipulates that the companies must make all reasonable efforts to obtain existing data and shall update the information in IUCLID, in particular new uses of the substance which could change the exposure to man and environment, new data obtained on toxicological and ecotoxicological effects where this is likely to be relevant to the evaluation of the potential risk presented by the substance.

For the priority substances which have undergone the risk assessment the "final" IUCLID data sheets will contain the validated data only, which lead to the conclusions in the risk assessment reports, accepted by the Member States Authorities.

AVAILABILITY OF IUCLID

4.1. IUCLID Data. The complete IUCLID database is provided to the Competent Authorities in the Member States in order for them to participate in the priority setting step and to carry out the risk assessment. However, IUCLID is also available to third parties such as research institutes and other interested parties.

4.1.1. Confidentiality. As shown above some data in Chapter 1 are regarded as confidential. The competent authorities are provided with the complete data and have to ensure confidential treatment. Industry and other interested parties can get the nonconfidential version of the database. This nonconfidential version is generated out of the master database under consideration of the following rules, which have been confirmed by the Industry Federations:

Chapter 1.1: degree of purity deleted.

Chapters 1.3 and 1.4: all entries deleted

Chapter 1.5: If less than four companies have reported, all information is deleted. If four or more companies have reported, the maximum values of the reported range are summed.

Chapters 1.6.1 and 1.6.2: Only the official labeling and classification following Directive (EEC) 67/548 is included if available, the provisional entries are not included in the record.

Chapter 1.7: Only when the use-pattern has been reported by four or more companies, is it included in the data sheet.

Chapters 1.9 and 1.13 have been reviewed for entries claimed as confidential.

4.1.2. Nonconfidential Export Files. The IUCLID data following the above mentioned rules are available in the IUCLID export format on CD-ROM from the ECB. The data can be imported from this CD-ROM to any other IUCLID installation. This methodology requires an Oracle installation but gives the opportunity to use the data to prepare one's own substance reports. Another possibility to get the IUCLID substance information is the so-called IUCLID "low-cost" CD-ROM:

4.2. The IUCLID CD-ROM. In order to achieve wide acceptability of the risk assessment reports, the risk assessment process must be transparent for all involved parties and the public. To give access to IUCLID without the necessity to install the Oracle database system, a CD-ROM system has been developed by the European Commission, which has had the retrieval software already installed on the CD-ROM as well. This CD system is MS-Windows based and easy to use. After the installation procedure the non-confidential IUCLID data sheets can be searched by EINECS-Nos., CAS-Nos. and synonyms and be displayed in the IUCLID standard printout format. Data sheets can be printed as from word-processing systems, via the clip-board (cut and paste) text can be copied from the data sheet into word-processing documents. However, the data contents in the system cannot be changed as in an original IUCLID installation.

The CD-ROM is available on request at the ECB for the price which covers the production cost (100 ECU/$125). The first edition contains all data sets which have been submitted in data-collection phase I. Further versions will contain the data collected in phase II and III and the summary risk

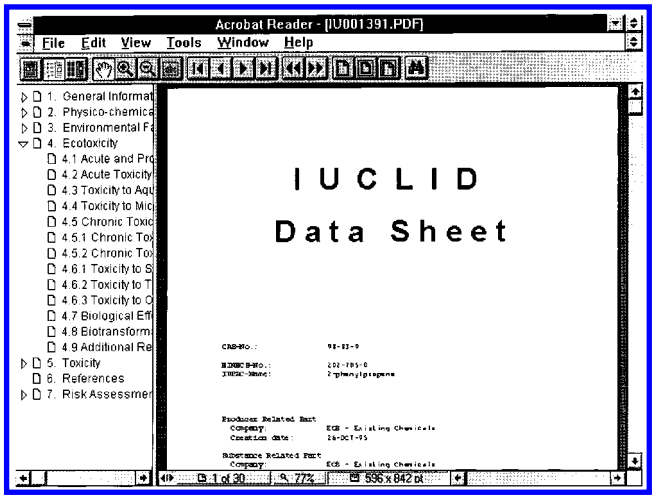

Figure 3. IUCLID CD-ROM.

assessment reports for priority substances. The CD-ROM is expected to be an accelerator for the improvement of the IUCLID data quality. Faulty data entries can easily be detected. Industry can correct them by sending an up-dated HEDSET data set.

4.3. Availability of IUCLID Software. The IUCLID software is the property of the European Commission, but the IUCLID software license is granted free of charge after approval by ECB for Industry and other interested parties. The new IUCLID users need only pay the installation, the media, and the Oracle license for the target system, if this target system is supported by the ECB. If a porting to a nonsupported target system is necessary, these extra costs have to be paid by the customer.

4.3.1. Supported Hardware/Operating Systems. IUCLID is currently operational on: IBM compatible PCs running MS-DOS or SCO-Unix, IBM RISC-6000 series with AIX, DEC-Alpha series with OpenVMS or DEC-UNIX, and SUN-sparc workstations with Solaris.

USE OF IUCLID

5.1. Current Installations. The IUCLID system has been installed in ca. 50 chemical companies and laboratories on the above operating systems. The Member States Authorities have had the software directly installed by the ECB, mainly on DOS-PCs. The OECD in Paris, the US/EPA Washington, and three Japanese institutions, dealing with chemicals control, have had a IUCLID installation. IRPTC-Geneva have a version for evaluation. At the ECB, IUCLID is running on an IBM AIX RISC-6000 in a secure area, several workstations allow access for ECB staff.

Within the risk assessment procedure IUCLID is used by different institutions for several purposes.

5.2. Industry. Here IUCLID can be used as an in-house products database, out of which the data sheets which have to be submitted to comply with the Existing Substances Regulation are created. Interface tools, programmed by consultants or staff, permit the use of IUCLID data sheets for the creation of Material-Safety-Data Sheets (MSDS). It is installed on distributed systems, often UNIX or VMS based, creating access for several departments.

Industry has organized the data collection to avoid duplication of work. The industry federations such as CEFIC have organized a voluntary action program to ensure contact between the lead companies and the cooperating companies that refer to the lead companies data sheet. Mainly the lead companies are using IUCLID instead of the HEDSET software when preparing large amounts of data sheets. The lead companies are using IUCLID to complete the data sheets containing the substance related part (see above) to be sent to the ECB and then send export files to the other companies on diskette, which can be loaded to their HEDSET installations.

5.3. European Chemicals Bureau. The ECB-IUCLID system is used to load all incoming data. After the loading process to the collection database, a data transfer to the distribution database is carried out. Here all data sheets for a specific substance are merged together to a single data sheet containing all data as submitted. Out of this distribution database the nonconfidential export-files and the database-files for the CD-ROM version are created. The IPS-program for priority setting has been programmed and refined on the same computer and creates a ranking of the substances in IUCLID, based on certain end-points, ordered by the degree of potential adverse effects to the environment and human health. Specific reports and queries on the entire database are developed here and made available for the Competent Authorities (CAs). The ECB is also using the IUCLID database in support of research activities in the field of environmental modelling and Quantitative Structure−Activity Relationships (QSAR).

5.4. Competent Authorities. The Competent Authorities have often received several installations in different institutes. One institution must coordinate the work on risk assessment. Here IUCLID is used to merge the parts of the data sheets edited, e.g., by the Health and Safety Authority on human health effects, together with the sections prepared by the Environmental Agency on effects on the environment. The outcome of the entire process will be a final IUCLID data sheet including chapter 7, the summary risk assessment report for each of the priority substances. This final data sheet, after having been discussed with the other Member States and OECD, will be part of the public IUCLID as well.

5.5. Other Organizations. The OECD Member Countries agreed to carry out a "Programme on the Co-operative Investigation of High Production Volume Chemicals".[10] The OECD Sponsor Countries use the HEDSET software to prepare the dossiers on the substances to be assessed. At the OECD headquarters in Paris these dossiers shall be loaded onto the IUCLID system. Japan's Ministry for Trade and Industry (MITI), the National Institute for Health Sciences (NIHS, Tokyo), and the National Institute for Environmental Studies (NIES, Tskuba) and in the United States the Environment Protection Agency (Washington) have gotten IUCLID systems. Data-exchange is now possible without language barriers, e.g., via Internet. At the IRPTC (Geneva) IUCLID is under evaluation if it can be used within the United Nations Environmental Programme (UNEP).

FUTURE DEVELOPMENTS

As the IUCLID database software is a tool to be used in a long-term process, backed by EU-Legislation, IUCLID has to be adapted to the technical and legislative progress.

A steering committee with experienced IUCLID users from Member States Authorities, Industry, and ECB staff has been established to define new requirements.

Planned developments include the capability to process the data sheets used in the Classification and Labeling process of dangerous substances. IUCLID will be capable of processing the additional data to be submitted for priority substances, the so-called base-set.

The chemical structure information in IUCLID will be visualized, and the improved query module will allow substructure searches.

The envisaged actions in the short term will be to concentrate on improving the user interface. IUCLID is currently based on simple screens and function keys without mouse operation. Within 1996 IUCLID will change its face to the standards set by Windows applications.

The software will be converted to a modern client/server architecture. PCs will be used as front-end machines, which shall be linked up to Oracle database servers. Stand-alone PCs are also further supported, though a lower performance has to be accepted.

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