Intraspecies factor

	GM	GSD	P95	
Our example:	-	-	-	
Kalberlah & Schneider, 1998	-	-	25	database derived
Baird et al., 1996	5.3	1.4	9	heterogeneity in rats
Slob & Pieters, 1998	1+3	1.6	10	assumption(P99)
Swartout et al., 1998	1+2.1	2	10	assumption
Price et al., 1997	1+2.1	2	10	assumption

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The response of humans to exposure of xenobiotic compounds may vary due to a number of biological factors, such as age, sex, genetic composition and nutritional status. The use of an intraspecies factor should protect the most sensitive human subpopulation with the average human being as a starting point.

The intraspecies factor cannot be < 1.

Semi-chronic to chronic

	GM	GSD	P95	
Our example:	2	4	20	database derived
Baird et al., 1996	2.0	2.1	7	database derived
Slob & Pieters, 1998	1.5	2.3	10	database derived/ assumed (P99)
Swartout et al., 1998	1+2.1	2	10	assumption
Price et al., 1997	1+2.1	2	10	assumption

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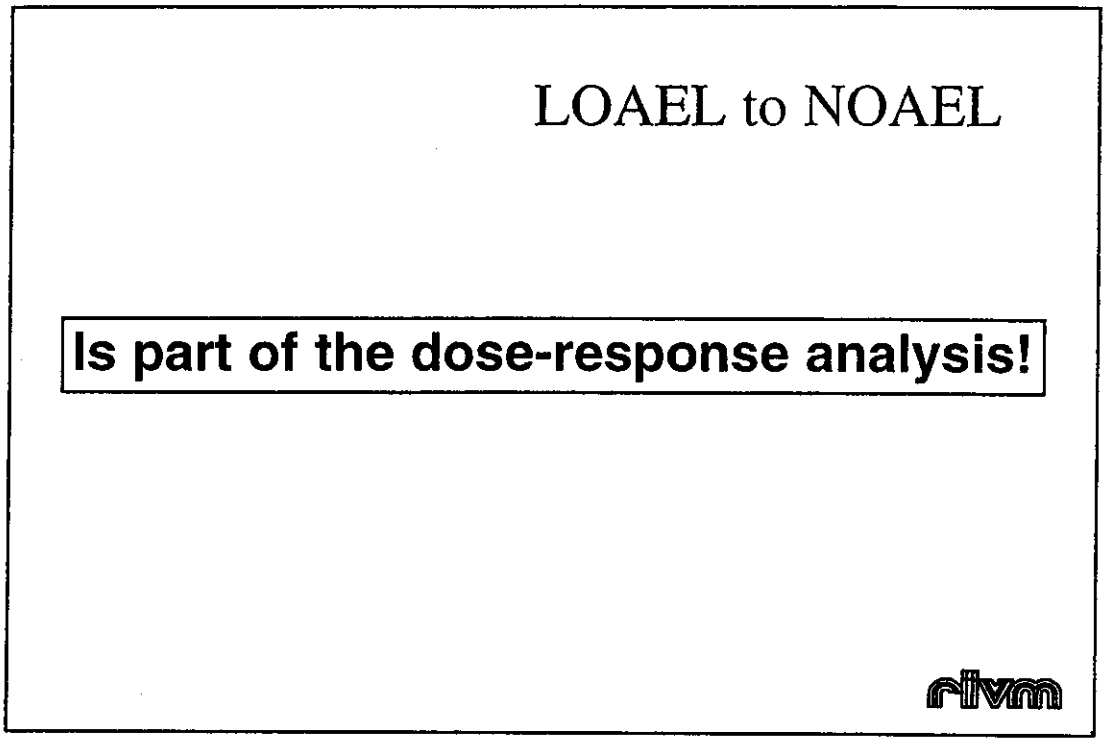
For the distribution of the extrapolation factor several studies comparing NOAELs from chronic and subchronic studies appear relevant (Weil and McCollister, 1963; McNamara, 1976; Rulis and Hattan, 1985; Kramer et al., 1995; Nessel et al., 1995; Kalberlah et al., 1997).

It should be noted that subchronic toxicological studies usually have smaller sample sizes compared to chronic studies (typically twice as small). Thus, the geometric mean ratios for the NOAELs assessed in the studies mentioned most likely overestimate the median of the distribution of the EFsubchronic.



The use of historical LOAEL/NOAEL-ratios to estimate a NOAEL from a LOAEL is questionable. Usually, doses in toxicological tests are spaced in fixed intervals and the observed distribution of LOAEL/NOAEL ratios therefore primarily reflects the historical frequency of use of various dose spacing. Therefore this factor can only be assigned using expert judgment in which the shape of the dose-response curve and the magnitude of the effect at the LOAEL is taken into account.

The true No-Adverse-Effect Level

$$NAEL_{true,human} = \frac{NAEL_{true,animal}}{EF_{true,interspec}\, EF_{true,intraspec}}$$

Approach this parameter:
- **Apply the modified benchmark concept [prob. distribution of CEDs]**
- **Assume that the true NAEL is the minimum of all Critical Effect Doses**

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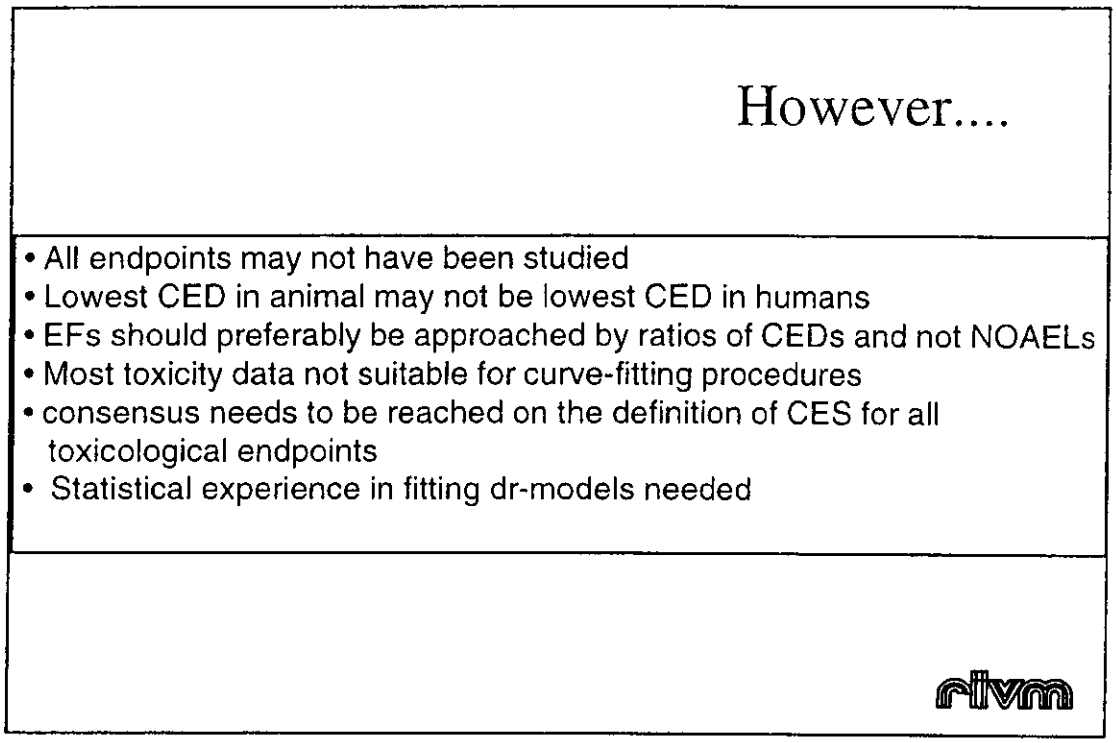
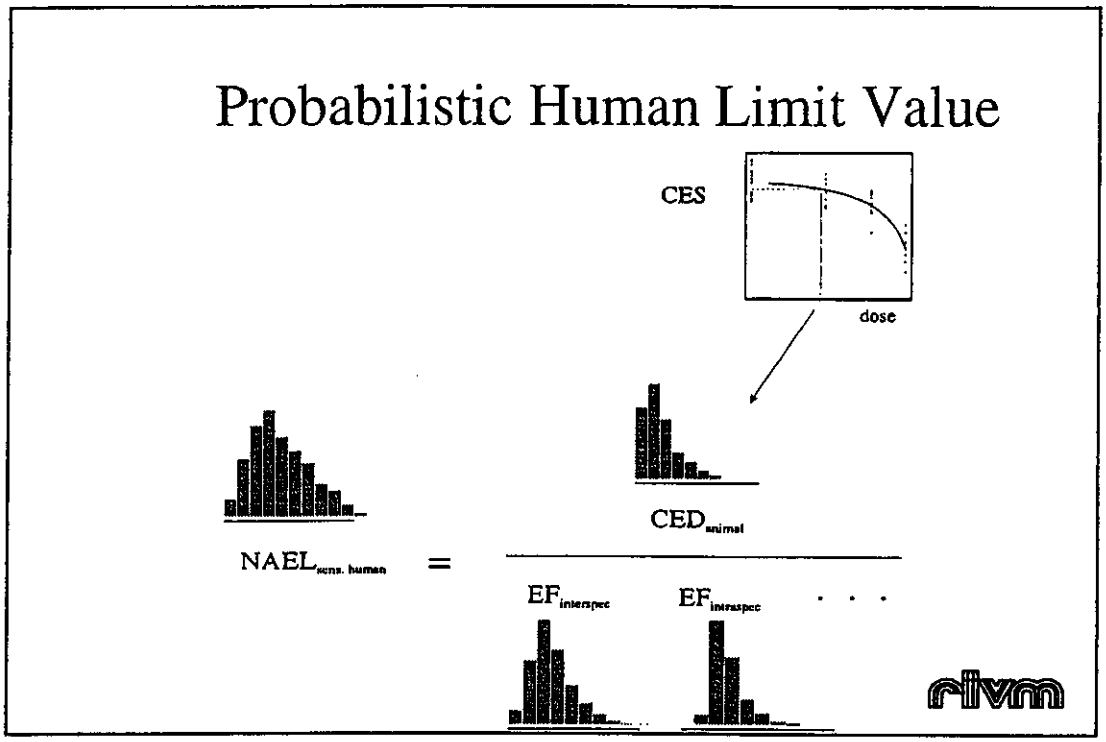
For the operationalisation of this concept, the question is how to estimate the NAELanimal and the EFs and the uncertainty distribution associated to each of them. The next slides will deal with the best approximation of the distribution of the NAELanimal . With regard to the EFs is can be argued that, although the value of the EFs are unknown for specific compounds, the extrapolation factors for the universe of all compounds must have a specific distribution. One might be able to estimate that distribution from historical data (e.g. from drugs). Ideally this should be done on the basis of ratios of the best approximations of the NAELtrue. More crude estimates of the distributions of EFs can be obtained on the basis of NOAELs as has been discussed already. It can be argued that the database derived distributions thus obtained are wider than would be obtained on the basis of the NAELtrue

CED = Critical Effect Dose (see next slide)

Benchmark method of Crump (1984)



Some drawbacks of the approach proposed.



Slob and Pieters (1998) proposed to find the complete uncertainty distribution of the CED estimate by bootstrapping: once a regression model has been fitted, Monte Carlo sampling is used to generate a large number of new data sets from this regression model, each time with the same number of data points per dose group as observed animals in the real experiment. For each generated data set the CED is re-estimated. Taking all these CEDs together results in the required distribution.

Since for each EF a certain distribution over all endpoints and substances is assumed it is possible to extrapolate any CED from one situation to the other. Thus, instead of choosing a single (most sensitive) endpoint from the animal data, each CED-distribution that is associated to a relevant endpoint is extrapolated to the distribution of the associated CED in the sensitive human (CEDsens.human) by probabilistic combination with the distributions of each EF. This results in a series of distributions for CEDsens.human, each related to another endpoint. Then this complete set of distributions can be considered as a basis for deriving a HLV, for example by choosing the lowest of each distribution's first percentile. It is noted that the assumption of complete independence of the various distributions of EFs will also be applied here.

Example 1

Results of the semi-chronic test of EXA[1]

Dose ($mg.kg_{bw}^{-1}.d^{-1}$)	Survival		mean body weight (g)		mean LDH level [2] (bb/ml)		incidence of UBH	
	m	f	m	f	m	f	m	f
0	19/20	19/20	480	264	1893	1427	0/20	0/20
400	20/20	20/20	480	266	2075	1584	0/20	0/20
1200	20/20	18/20	453*	274	2442*	1971*	2/20[3]	3/20[3]
4800	19/20	15/20*	346*	252*	4637*	3866*	15/20[4]	13/20[4]

[1] LDH = lactate dehydrogenase, UBH = urinary bladder mucosal hyperplasia, m = males, f = females

[2] LDH-levels were determined in 10 rats/sex/dose.

[3] very slight

[4] very slight (3m, 9f), slight (3m, 3f), moderate (6m, 1f), marked (3m, 0f)

* = statistically significant (t-test)

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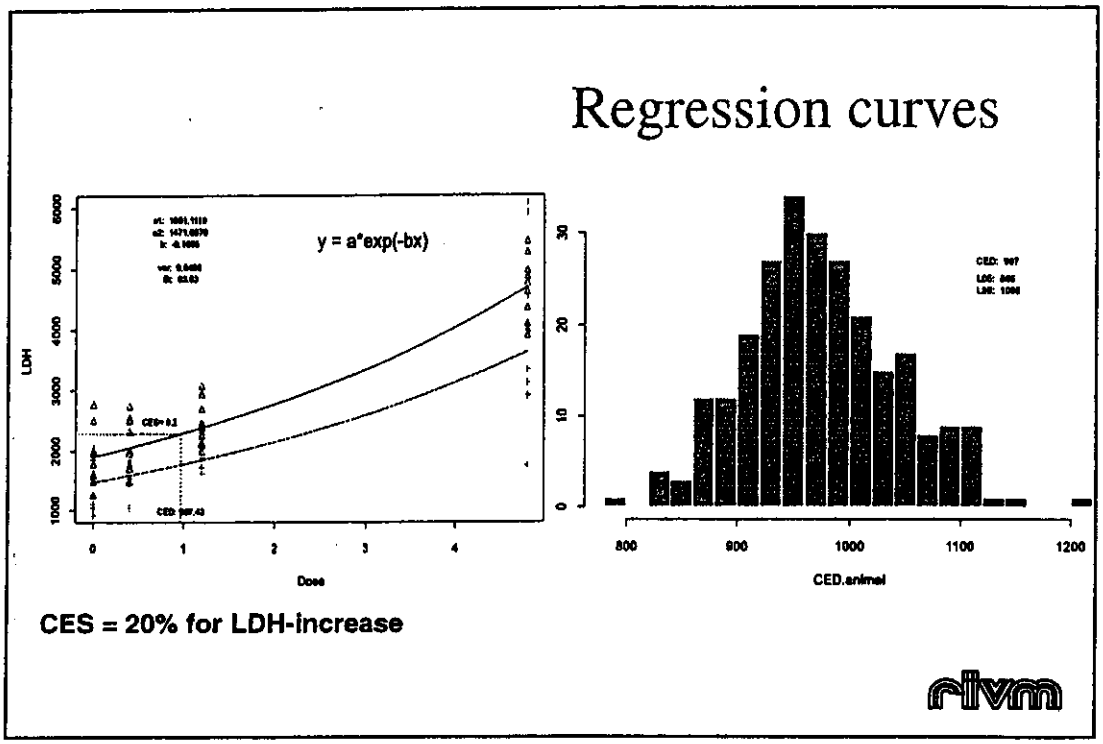
The different approaches discussed in previous chapters will now be applied to an example substance EXA. EXA has an oral NOAEL of 400 mg.kgbw-1.d-1. This NOAEL was derived in a 3-months test (semi-chronic) in rats. This example will only include extrapolation from experimental animals to average humans (AF1), from average humans to sensitive humans (AF2) and from a semi-chronic toxicity test to a chronic test (AF3). In all approaches the target is to protect all human beings and therefore the 95th percentile (P95) of distributions of assessment factors is selected for the derivation of the Human Limit Value (HLV) for man.

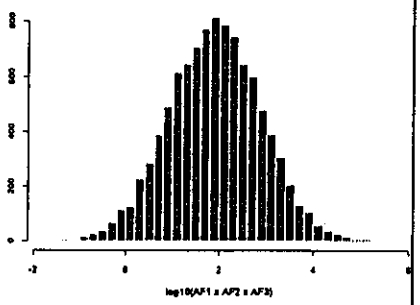


No difference in sensitivity between males (triangles) and females (plusses), so the data can be pooled for the derivation of the CED.

A problem is the choice of the CES. Is 20% critical?

Monte Carlo for AFtot for EXA

Assessment factor	Distribution	Geometric mean	Geometric standard deviation
AF_1: interspecies, kinetics	discrete value	4	-
interspecies, residual	lognormal	1	6
AF_2: intraspecies	discrete value	10	-
AF_3: duration of exposure semi-chronic to chronic	lognormal	2	4



GM = 80
GSD = 9.6
P87 = 1000
P95 = 3300

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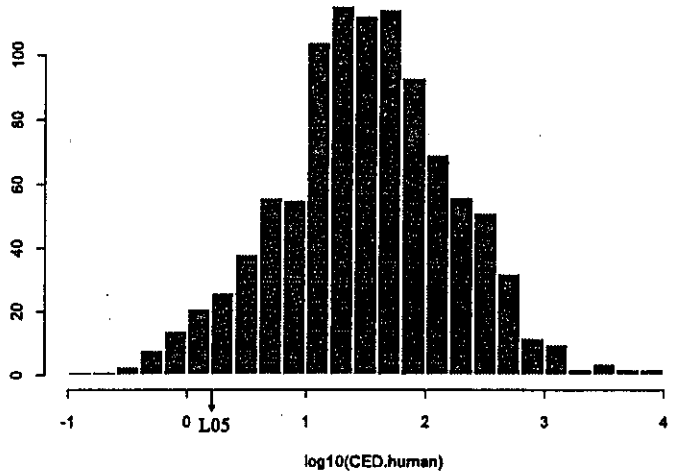
This slide shows the probabilistic combination of (distributions of) assessment factors

CED-human for EXA



P5 = 0.25 mg.kg^{-1}bw.d^{-1}
AFtot relative to NOAEL is 1600

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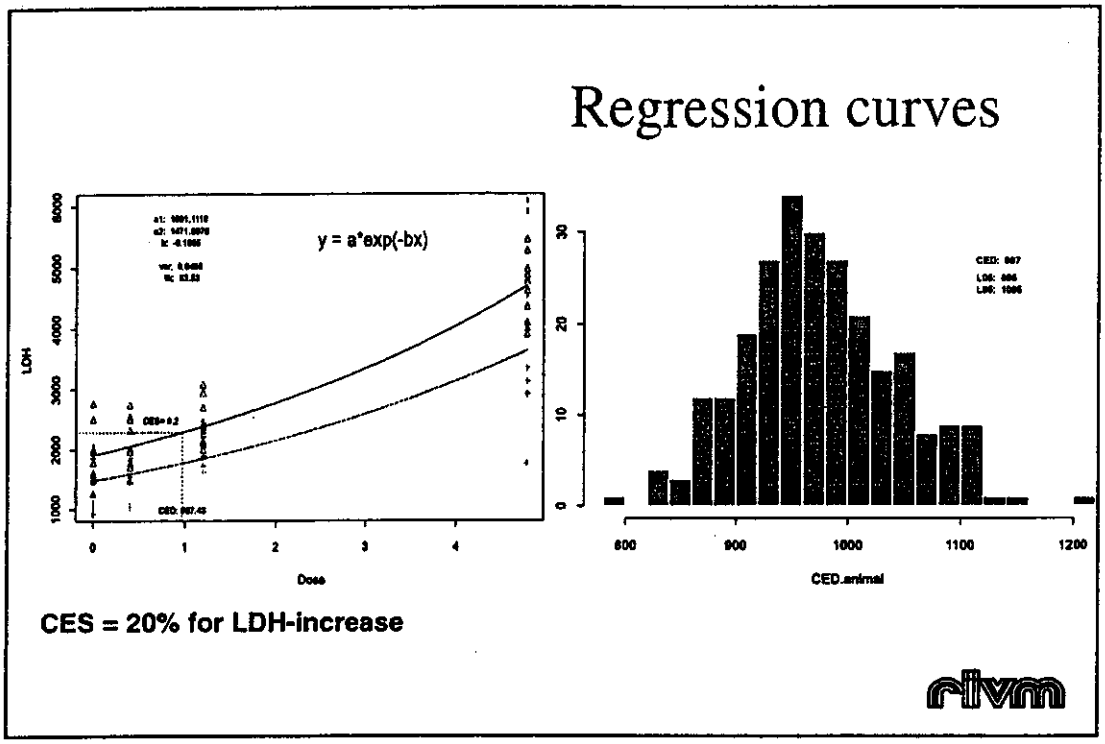
Conclusions and recommendations

- Long-term goal: probabilistic RA?

- Stepwise-implementation
  - Investigate further distributions of AFs
  - Investigate further probabilistic benchmark procedure
  - Investigate further probabilistic exposure assessment
  - Communication with risk managers

- Further research:
  - Interspecies extrapolation need further analysis of variability in toxicokinetics (scaling) and pharmacodynamics
  - Intraspecies: research into human variability
  - Refinement of extrapolation for study period
  - CES-derivation



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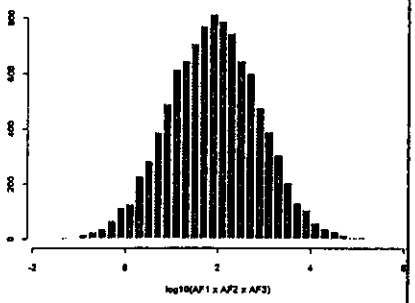

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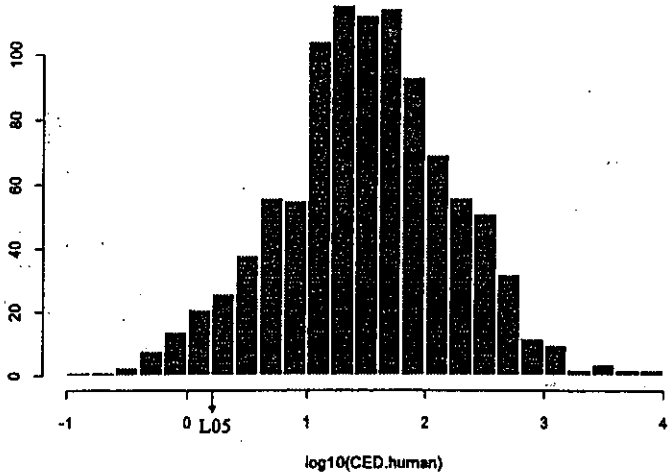

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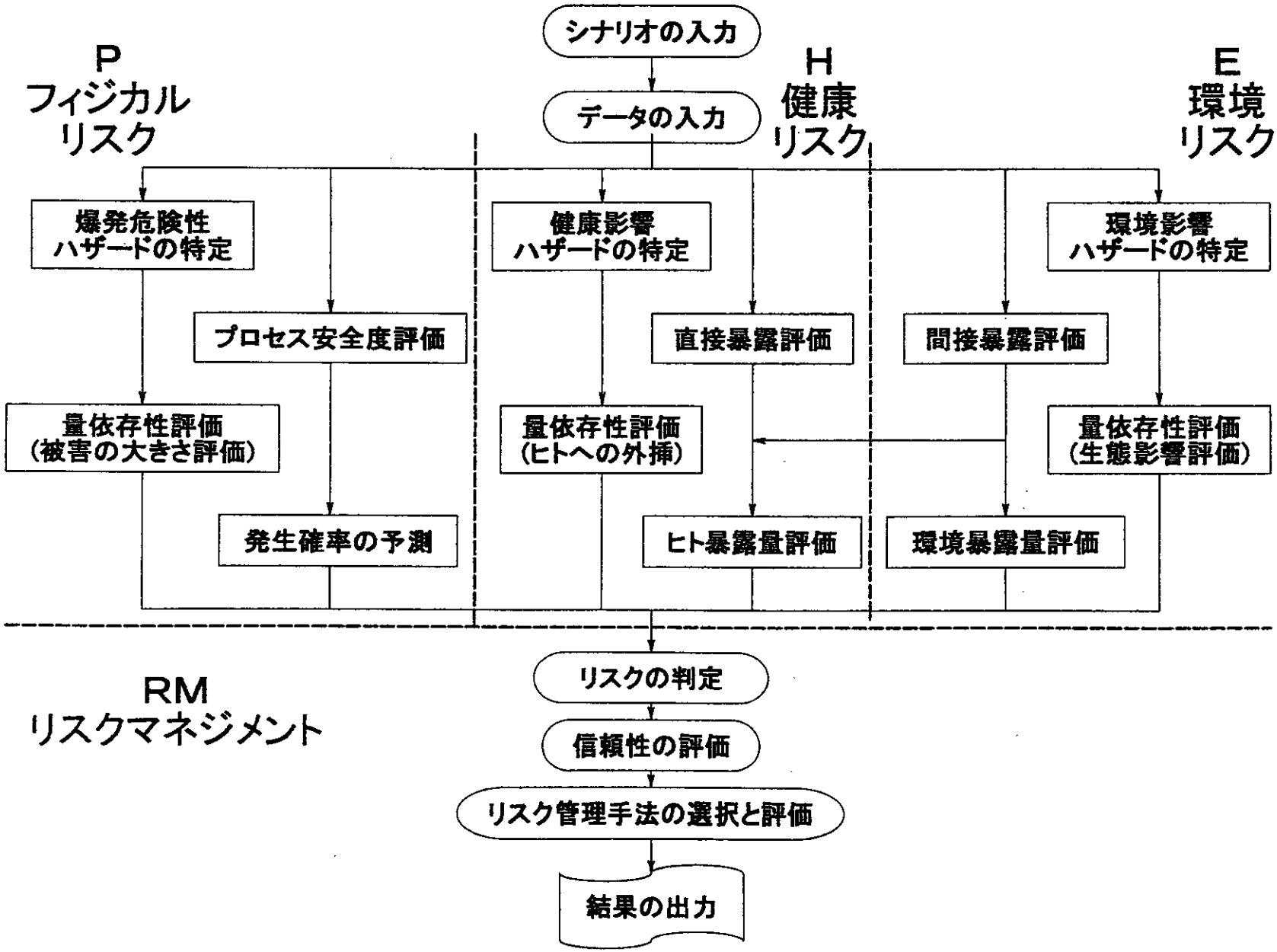
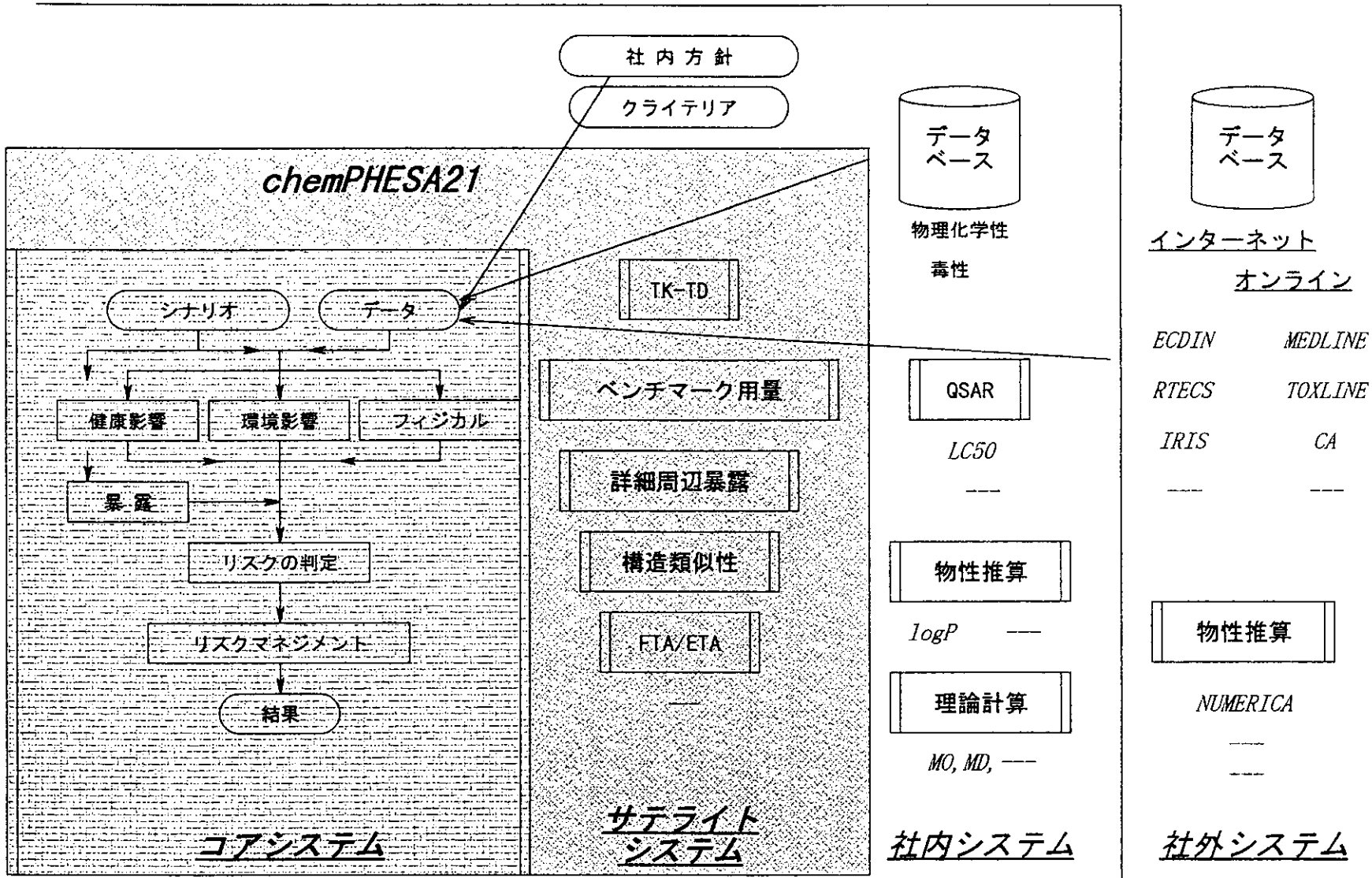
リスクアセスメント・システム（Chem PHESA－21）について

花井　荘輔

日本化学工業協会化学物質総合安全管理センター

化学物質のリスクアセスメント概念図





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