
REACH: Jongleren met toxicologische kengetallen

Hoe is de uitwerking van de REACH-regels door de industrie?



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Onderwerpen

1. Organisatie
2. Vaststellen hazards
3. Afleiden DNELs
4. Opstellen Exposure scenario's
5. Risk Management
6. Conclusies



Organisatie Algemeen

Registraties cruciaal voor continuering van business.
Doelstellingen sluiten aan bij AN responsible care en sustainability ambitions

- AkzoNobel registraties: fase 1 – 2010: Ca. 140 (lead 60)
fase 2 – 2013: Ca. 150 (lead 50)
- Veelal consortia en SIEF contracten
- Zeer uitgebreide range van activiteiten
(marketing, budget, contracten, sample archive, library, identity & purity, PhysChem, fate & ecotox, tox, gebruik en blootstelling, informatie, coördinatie, project management)

➡ Teamwerk van specialisten noodzakelijk



Organisatie Uitdagingen en problemen

Dossier projectleider en project team per stof

- Organisatie en coordinatie
- Gegevens (Volumina; CMR / PBT status) niet altijd direct voorhanden
- Veel producten op de markt; product \neq stof
- Stof identiteit
- Tijdsdruk
- Communicatie
- Harmonisatie & consistentie bewaking



Consortium submission

Substance	CAS	EINECS			New substance name	CAS	EINECS	Registration deadline
1H-Imidazole-1-ethanamine, 4,5-dihydro-, 2-nortail-oil alkyl derivs.	68442-97-7	270-500-3	C18:1, C18:2	} Merge	Fatty acids, C18 unsat, reaction products with diethylenetriamine	1226892-43-8	none	2010
Fatty acids, C12-18 and C18-unsatd., reaction products with diethylenetriamine	91001-82-0	292-855-3	C18:1, C18:2					
Fatty acids, vegetable-oil, reaction products with diethylenetriamine	68153-72-0	268-894-7	C18:1, C18:2					
Tail oil, reaction products with tetraethylenepentamine	68655-22-6	271-417-5	C18:1, C18:2	} Merge/Split	Fatty acids C18 unsat, reaction products with tetraethylenepentamine	1226892-45-0	none	2010
Fatty acids, tail-oil, reaction products with tetraethylenepentamine (imidazolines)	68953-36-6	273-201-6	C18:1, C18:2					
Fatty acids, tail-oil, reaction products with tetraethylenepentamine	68953-36-6	273-201-6	C18:1, C18:2					
Fatty acids, vegetable-oil, reaction products with pentaethylenhexamine	93572-25-9	297-455-2	C18:1, C18:2	} Merge/Split	Fatty acids C18 unsat, reaction products with Pentaethylenhexamine	1224966-13-5	none	2010
Fatty acids, tail-oil, reaction products with polyethylenepolyamines	68910-93-0	272-756-1	C18:1, C18:2					
Fatty acids, tail-oil, reaction products with polyethylenepolyamines	68910-93-0	272-756-1	C18:1, C18:2					
				} Merge/Split	Amides, fatty acids C18 unsat, reaction products with polyethylene amines	1226892-50-7	none	2010
						Fatty acids, C18 unsaturated, reaction product with ammonia-ethanolamine reaction by-products	1224966-15-7	none



Hazard assessment

Verzamelen van gegevens

- Bepalen identiteit en mogelijk scope van grouping
- Profiling (o.a. OECD Toolbox) en QSARs
- Evaluatie en beoordeling rapporten en literatuur
- Datagap analyse en voorstel test strategie

➔ Test plan

Doel:

- Correcte classificatie
- Identificatie mogelijk gevaarseigenschappen en vaststellen van (voorlopige) DNELs
- Voorgestelde studies
- Dossier en CSA opstellen



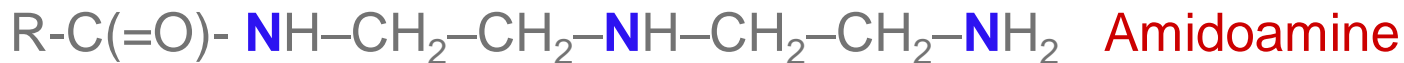
Hazard assessment Voorbeeld test plan aanpak

Imidazolines

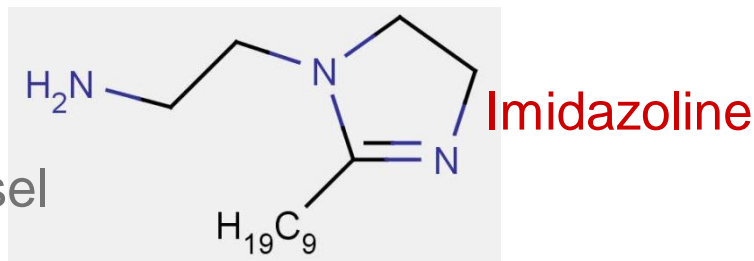
FA + polyamine:



FA + polyamine:



Upon heating ring forming:



In principe altijd een mengsel



Hazard assessment Grouping? Imidazolines

Test plan – Human Health

Based on (avg.) EA:	DETA	DETA	TETA	TEPA	TEPA (TETA, TEPA, PEHA) (solvent 5-15%)	PEHA	(PEHA) Poly: (TETA, TEPA, PEHA, poly)	Poly (PEHA, poly)	DETA+ TETA+ AEP+D EA+ TEA	Poly (residues)	(PEHA) Poly: (TETA, TEPA, PEHA, poly)
Substance number(s)	1 (=8)	12, 13	9, 17	2, 11, 14	3	10	15	5	16	6	4
reactant resin acids [%]	≤ 2	-	-	≤ 2	≤ 2	≤ 2	≤ 2	≤ 2	-	≤ 2	≤ 2
% residual free FA	2			1.6						0.8	
% residual free EA	3	8-10; 14-17	17-20 10-16	~2; 10-12; <1	~2	7-12	<10	<5	<5	~2	<5
FA:EA	2:3	1:1 3:5	3:5 1:1.13	1:1 3:4 2:1	2:3	3:4	1:1	1:1	1:1	2:3	1:1
amide:imidazoline	45/55	45/55 55/45	55/45 30/70	42/58 45/55 100/0	26/74	45/55	30/70	58/42	60/40	38/62	100/0
Temperature	H	H	H	H	H	H	H	H	H	H	L



Hazard assessment Reprotox strategie

Teststrategie reprotox:

1. OECD 422 & test proposal volledige testen
2. Direct proposal volledige testen
3. Extended OECD 422









DNELs – Hazard data

DNELs:	route	Workers 70 kg	Population 60 kg	(Generally) tested	Classification
Acute / Short-term – systemic effects	Oral	n.a.	n.a.	Y	Acute - oral
	Dermal	mg/kg bw	mg/kg bw	y/n	Acute - dermal
	Inhalation	mg/m ³	mg/m ³	N	Acute - Inhalation
Acute / Short term – local effects	Dermal	mg/cm ²	mg/cm ²	Y	Dermal Corrosion/irritation
	Inhalation	mg/m ³	mg/m ³	N	Acute - Inhalation
Long-term exposure – systemic effects	Oral	n.a.	mg/kg bw	Y	STOT-RE
	Dermal	mg/kg bw	mg/kg bw	y/n	STOT-RE
	Inhalation	mg/m ³	mg/m ³	N	STOT-RE
Long-term exposure – local effects	Dermal	mg/cm ²	mg/cm ²	y/n	STOT-RE?
	Inhalation	mg/m ³	mg/m ³	N	STOT-RE?
Eye				Y	Eye irritation
Sensitisation	Dermal			Y	Dermal sensitisation
	Inhalation			N /cr	Respiratory sensitisation
Genotoxicity				Y	Mutagenicity
Carcinogenicity				?	Carcinogenicity
Reproduction	Fertility			Y	Reproductive toxicity
	Developmental			Y	Reproductive toxicity
	via lactation			Y	Reproductive toxicity
Aspiration				N	Aspiration hazard
Narcotic effects / RTI				N	STOT-SE Cat.3
Toxicokinetics	only for CSA				



Classificatie en labelling

Notified classification and labelling according to CLP criteria

Classification			Labelling		Specific Concentration limits, M-Factors	Notes	Number of Notifiers 	Joint Entries 	View 
Hazard Class and Category Code(s)	Hazard Statement Code(s)	Hazard Statement Code(s)	Supplementary Hazard Statement Code (s)	Pictograms Signal Word Code(s)					
Eye Irrit. 2	H319	H319		GHS07 GHS08 Wng			24		
Carc. 2	H351	H351							
Acute Tox. 4	H302	H302		GHS07 GHS08 Dgr			1		
Acute Tox. 4	H312	H312							
Skin Irrit. 2	H315	H315							
Eye Irrit. 2	H319	H319							
Acute Tox. 4	H332	H332							
STOT SE 3	H335	H335							
Carc. 1A	H350	H350							
Eye Irrit. 2	H319	H319		GHS07 Wng			1		



Classificatie en labelling



Skin Corrosive category and subcategories			
		Corrosive in ≥ 1 of 3 animals*	
	Corrosive subcategory	Exposure	Observation
Category 1: Corrosive	1A	≤ 3 minutes	≤ 1 hour
	1B	> 3 minutes - ≤ 1 hour	≤ 14 days
	1C	> 1 hour - ≤ 4 hours	≤ 14 days

DSD R35 Corrosief na 3 minuten → GHS Cat. 1A



DNELs - Onzekerheden

Relevance, complexity, costs



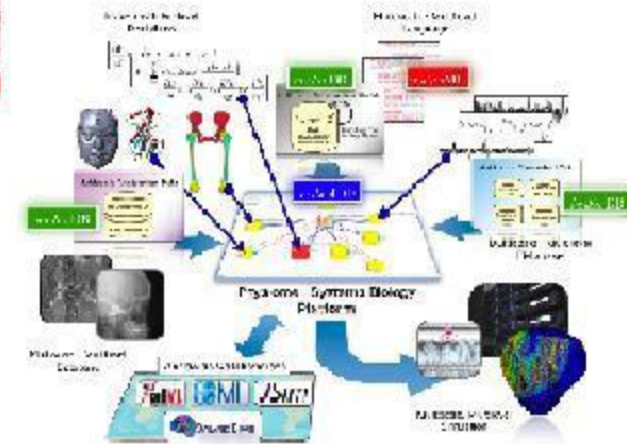
Human data



Animal data



In vitro data



Non-testing

Uncertainty



DNELs – Assessment Factors

0 modification of dose descriptor

route-to-route: Algemeen AF = 1
oral → inhal. AF = 2

Haber's wet voor blootstellingsduur

I Interspecies differences

AF = Allometric scaling + 2.5
Rat → human: AF = $4 \times 2.5 = 10$

II Intraspecies differences

(polymorfisme, leeftijd, sex, gezondheid, voeding, gedrag)

Workers: AF = 5; Population AF: = 10

III Differences in duration of exposure

28-d → 90-d: AF = 3

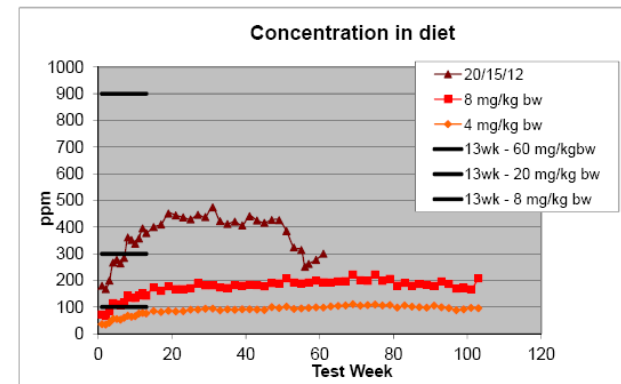
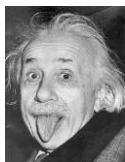
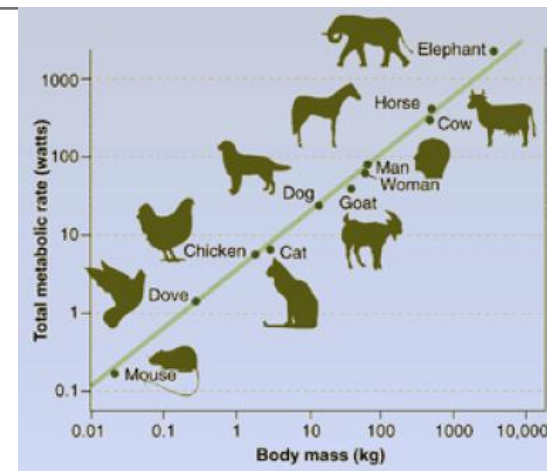
90-d → chronic: AF = 2

IV Issues related to dose-response

LOAEL → NOAEL: AF = 3

V Quality of whole database

Read-across/*in vitro* / QSAR



POD - Selectie NOAEL voor DNEL

Study	NOAEL mg/kg bw/d	LOAEL mg/kg bw/d	Effects
Oral			
Repeated dose 90-day rat (Diet: 644, 1287, 2574 ppm)	42 - 49 (644 ppm)	84 - 96 (1287 ppm)	<i>Lower food consumption and body weight gain. Distended coecum with faeces; histiocytosis and mastocytosis in the mesenteric lymph nodes.</i>
90-day dog (Diet: 122, 243, 486 ppm)	15-18 (486 ppm)		<i>No signs of toxicity were observed in any dose group. (Highest attainable concentration due to palatability)</i>

Chronische studie resulteerde tot een zelfs iets hogere NOAEL

Ingediend: $DNEL = 46 (42-49) / 100 = 0.46 \text{ mg/kg BW/day}$

Autoriteiten: $DNEL = 15/100 = 0.15 \text{ mg/kg BW/day}$



POD - Selectie NOAEL voor DNEL

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Ingediend: $DNEL = 46 (42-49) / 100 = 0.46 \text{ mg/kg BW/day}$
 Autoriteiten: $DNEL = 15/100 = 0.15 \text{ mg/kg BW/day}$

	NOAEL mg/kg bw	DNEL (AF = 100) mg/kg bw	AF	DNEL mg/kg bw
Rat	46	0.46	$4 \times 2.5 \times 10 = 100$	0.46
Dog	15	0.15	$1.4 \times 2.5 \times 10 = 35$	0.43



DNELs – Assessment Factors

- AF afhankelijk beschikbare gegevens / default
 - Alleen 28-dagen studie: NOAEL = 1000 mg/kgBW/d
 - AF: $10 \times 10 \times 6 = 600$
 - DNEL = 1.7 mg/kgBW/d
(ca. 0.01% in voedsel; 0.1 ml op huid)

➔ 'Informed' AF



DNELs – Assessment Factors

			Systemic		Local	
			REACH TGD	ECETOC	REACH TGD	ECETOC
0	- modification of dose descriptor	Route-to-route extrapolation: Oral to inhalation	2	no prop.		
I	- Interspecies differences	Allometric: rat-> man	4	4	1	1
		'Remaining differences'	2.5	1	2.5	1
II	- Intraspecies differences	Worker	5	3	5	3
		General population	10	5	10	5
III	- Differences in duration of exposure	Sub-acute to sub-chronic	3	3	3	1
		Sub-chronic to chronic	2	2	2	1
		Sub-acute to chronic	6	6	6	1
IV	- Issues related to dose-response	Reliability of doseresponse, LOAEL/NAEL extrapolation and severity of effect	≥1 -> 3 -> 10	3	≥1	
V	- Quality of whole database	Completeness and consistency	≥1		≥1	
		Reliability of alternative data (e.g. read-across)	≥1		≥1	



Exposure scenario's

1	Green	Believed (by JB) to be biocidal application and thus considered as being already registered for REACH. I did not check the SU and PC indicated							
2	Orange	Believe (by JB) to be medicinal / API and thus exempted from registration. I did not check the SU and PC indicated							
3	Red	Information received from the customer							
4	Blue	Information filled in (PVL, TR, PR) for customers who are also marked in red							
5	Black	Information filled with no details received from the customer and in the line below in purple, my suggestion when relevant (and to be discussed)							
6									
7		For some customers present in several countries (eg Sun chemicals), I filled in info only in one country, the most relevant one (eg UK for Sun)							
8									
9									
10	Customer	Deb. Country	SU	PC	PROC	AC		Product	Use description
11		Austria	SU8	PC19, 32	PROC 3,4,8a, 8b		ERC1, 6c	PTSA and KF 9S	
12		Austria	SU9	PC19	PROC4				
13		Austria	SU3	PC26					
14		Austria	Refer to the letter received: no number according to REACH SU, PC and PROC classification but explanation of the use						
15		Austria	SU1	PC8	PROC 11			Halamid BPD	
16		Austria	SU3	PC26					
17		Austria	SU1	PC8					
18		Austria	SU9	PC19					
19		Austria	SU3, 10	PC18	PROC 1, 2, 3, 5, 8a, 8b, 9, 10				
20		Belgium	SU9	PC19	PROC4				
21		Belgium	SU9,10,20,22	PC19,21,29	PROC3,9,15		ERC6a	PTSC	
22		Belgium	XXXXX	XXXXX	XXXXX				
23		Belgium	SU9	PC34	PROC4				
24		Belgium	SU9, 10	PC1, 5, 9, 18, 19, 32, 3	PROC4, 5, 9, 14	AC0	ERC2, 05, 6A, 6D	OPTSA	
25			another long list of SU, PC and PROC is available, refer to document received						
26		Belgium	BIO	PC8	PROC8/11			Halamid BPD	
27		Belgium	SU9 (NACEC 20)	PC19	PROC4		ERC6a	PTSC	
28		Belgium	SU9	PC19	PROC4			Halamid PG	
29		Belgium	BIO	PC8	PROC 14			Halamid	
30		Belgium	BIO	PC8	PROC8/10/11			Halamid	
31		Belgium	SU10	PC18	PROC5/10				
32		Belgium	SU10	PC18	PROC5/10				
33		Belgium	XXXXX						
34		Brazil	SU3,10,22, 21	PC9,35	PROC1,3,4,5,7,8b,9,10,11,15		ERC2,4,5,8a,8c,8d,8f	OPTSA for their final product resin fluorescent pigment	
35		Bulgaria	SU9	PC19				PTSC	
36		Czech Republic	SU3	PC29				Halamid PG	
37		Czech Republic	SU9	PC19					
38		Denmark	SU1	PC8	PROC 11			Halamid BPD	
39		Denmark	SU1	PC8	PROC 11			Halamid BPD	
40		Denmark	SU3 NACEC21	(PC20?) Used in prod	PROC 3		ERC6a	PTSC	
41		Denmark	SU3 (NACEC21)	PC19,29	PROC3, 4		ERC4,6a,2		
42		Denmark	SU1	PC8	PROC 11			Would this really be a biocide or P Halamid BPD	
43		Denmark	SU3, 10	PC18	PROC 1, 2, 3, 5, 8a, 8b, 9, 10				
44		Estonia	SU1	PC8	PROC11			Halamid BPD	



Exposure scenario's

Informatie zeer moeizaam. Vaak onbekend, soms
confidentieel

“Waar wordt stof/product precies voor gebruikt?”

“Hoe wordt precies met de stof omgegaan?”

“Hoeveel wordt er gebruikt?”

“Hoe lang duurt het gebruikt – interval - periodiek?”

“Welke RMMs worden reeds toegepast? (en werken ze)”

Praktischer is om van standaard scenario's uit te gaan.



GES – Generic Exposure Scenario's

Exposure Scenario	Description	Human exposure due to:	Environmental emission due to:
ES 1	Production of substance (not for communication with Akzo customers)	Charging/discharging of pure substance; laboratory activities	Spillages due to the production process, cleaning processes
ES 2	Formulation of substance (Adding substance to liquid or solid to formulations)	Charging/discharging of substance (Distribution: loading and repacking of substances); laboratory activities	Spillages due to the formulating process, cleaning processes
ES 3	Use in synthesis as a process chemical (not as a reactant) and as an intermediate	Charging/discharging of substance; laboratory activities	Emission to industrial activities to a sewer system
ES 4	Industrial and professional use of substance in spraying formulations	Spraying formulations;	Wide dispersive use
ES 5	Industrial and professional use of substance in non-spraying formulations	Non-spraying formulations	Wide dispersive use
ES 6	Industrial and professional use of substance in laboratory settings (small scale)	Laboratory activities	Spillages due to laboratory process, cleaning processes
ES 7	Use of substance in consumer products		Wide dispersive use



GES – Generic Exposure Scenario's

	Life cycle stage PTSA (CAS number 70-55-3)					
	Production (not requested)	Formulation and distribution	End use			
	ES1	ES2	ES3	ES5	ES6	ES7
Title	Generic ES for the production of substance including transfers and laboratory activities	Adding substance to liquid and solid formulations including distribution and associated laboratory substance. Distribution: loading and repacking of substances.	Use in synthesis as a process chemical (not as a reactant) and as an intermediate including transfers and laboratory activities	Industrial and professional use of substance in non-spraying formulations	Use of the substance within small scale laboratory settings	Consumer use (private household)
PROCs covered (see Echa guidance R12)		8a, 8b, 9, 10, 15, grinding	1, 2 3, 4, 8a, 8b,9, 10, 15	4, 8a, 8b, 6,10, 15,	10, 15	Not applicable
ERCs covered (see Echa guidance R12)		2	6a			
PC covered (see Echa guidance R12)		not applicable	not applicable	not applicable	21	1
SU covered (see Echa guidance R12)		3, 10	3, 8, 9	3, 5	3, 22	22/21
AC (article category) (see Echa guidance R12)						5(?)
X: exposure scenario (examples)						
Description						
Formulation/Distribution (including possible grinding)		X				
Intermediate			X			
Adhesives/Sealants (gluing textile layers) Use as plasticizer (Grinding applied)				X		X
Laboratory use					X	



Selectiecriteria stoffigheid en vluchtigheid

Information: TRA ECETOC Technical Report No. 93 (2004)

Help on fugacity selection criteria			
General description	Relative dustiness potential	Typical materials	TRA Selection Value
Not dusty	1	Plastic granules ^a , pelleted fertilisers	Low
Slightly dusty	10 - 100 times dustier	Dry garden peat, sugar, salt	
Dusty	100 - 1,000 times dustier	Talc, graphite	Medium
Very/extremely dusty	More than 1,000 times dustier	Cement dust, milled powders, plaster, flour, lyophilised powders, (process fumes ^b)	High
<p>^a Exposures to materials where a substance is contained and bound in a matrix (e.g. pigment within a plastic, filler within paint) should also be included in this category. Although the real exposure is actually determined by a combination of physical form and the bioavailability of the substance within the matrix, because the bioavailability is very low under such circumstances, then this will result in a low exposure potential.</p> <p>^b Process fumes (e.g. rubber, welding, soldering) behave like gases and would be considered within this category if exposures to such complex mixtures are considered in any risk assessment.</p>			



Exposure assessment

Ter beschikking staande modellen

- Stoffenmanager
- ECETOC Targeted Risk Assessment / CEFIC GES
- Advanced REACH Tool (ART)
- ConsExpo
- Additionele specifieke modellen indien nodig

Bedenk:

- Modellen zijn altijd conservatief
- Ieder model kent beperkingen
- Specialisten nodig voor adequate toepassing



Generic ! → CEFIC-GES

Gebaseerd op ECETOC TRA – voor professionele gebruikers

We berekenen *worst case (default values)* blootstellingen m.b.v ECETOC TRA, die weer worden ingevoerd in CEFIC-GES.

Voordelen:

- Grote set standaard zinnen (eenvoudiger voor vertalingen)
- Grote range van Contributing Scenarios (CSs) beschikbaar
- Gestandaardiseerde set van RMMs
- Genereert een ES volgens conform ECHA eisen die direct in Word overgebracht kan worden.
- Uitgebreid overzicht van alle PROCs, CSs en RMMs voor CSR
- Snel proces

De uitkomsten worden herhaald totdat een veilig niveau bereikt wordt (i.e.: $\sum RCR < 1$ voor oraal + inhalatoir + dermaal) door wijzigen van operational conditions (OC's) en toepassen RMM



Risk management

Risk management onder REACH richt zich op de reductie van blootstellingen waarvan is aangegeven dat deze niet veilig zijn, via:

- Bron aanpak (vervanging; vloeistof ipv stof)
- Technische maatregelen (machine beveiliging)
- Algemene maatregelen (werkwijze veranderen)
- Persoonlijke beschermingsmaatregelen

ESD's zijn algemeen, maar Elke industriële hygiënecontrole probleem is uniek

- Controleer altijd de effectiviteit van de maatregelen
- Meten is weten
- Vooral als blootstellingen geheel gebaseerd zijn op model schattingen, moeten blootstellingen gecontroleerd worden als RMM zijn geïmplementeerd.



Conclusions

- Gebruik geboden en beschikbare guidance en tools
- Blijf gezond verstand gebruiken.





3/16/2004 USA TODAY

A jury awarded \$20 million Monday to a Missouri factory worker who says his lungs were destroyed by the butter flavoring used in microwave popcorn.

