

Universiteit Utrecht

UU – Faculty of Veterinary Medicine

Maken wij ons terecht zorgen over het gebruik van bestrijdingsmiddelen?

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All substances are poison: there is none which is not a poison. The right dose differentiates poison from a remedy

It is the *timing* of the dose during life that makes the poison.

(Paracelsus 1493-1541)

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“The problem with toxicology is not the practicing toxicologists, but chemists who can detect, precisely, toxicologically insignificant amounts of chemicals”

Rene Truhaut, University of Paris (1909-1994)

Detectie grens tegenwoordig: **femtogram = 10⁻¹⁵ gram**

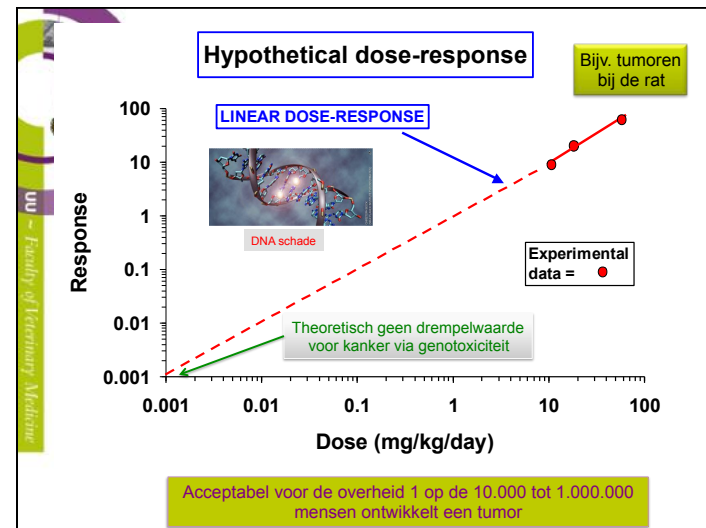
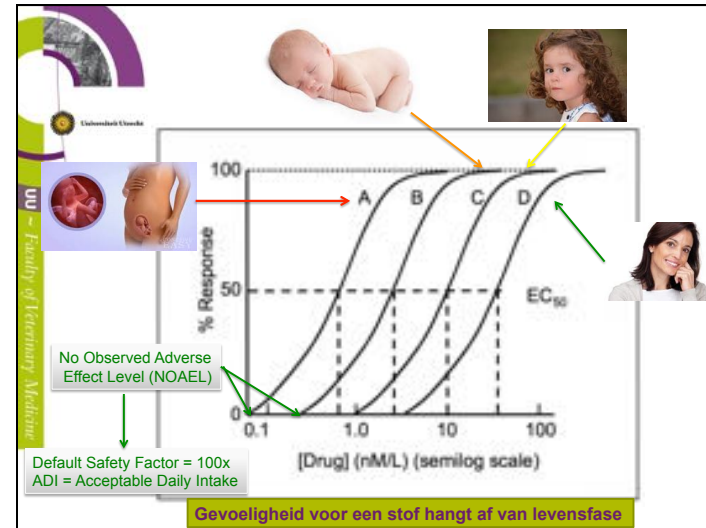
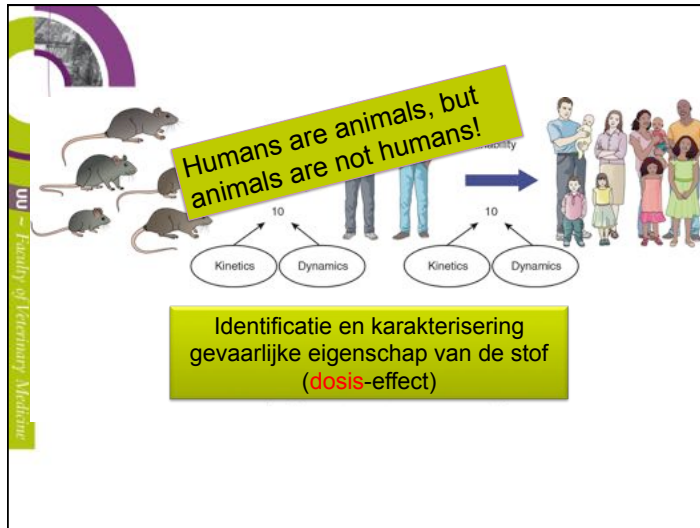
Gewicht van 1 (!) darmbacterie (E.coli)

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Hazard vs. Risk

- **Hazard**
 (potentieel gevaarlijk voor gezondheid):
 = intrinsieke eigenschap van een stof
- **Risk (risico):**
 = waarschijnlijkheid dat die gevaarlijke eigenschap zich manifesteert bij een bepaalde blootstelling



International Agency for Research on Cancer
World Health Organization

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Carcinogenicity of tetrachloro-*p*-phos, parathion, malathion, diazinon, and glyphosate

News

Bestrijdingsmiddelen kankerverwekkend?

Hazard (Not Risk!) Characterization
Class 2B: Possibly carcinogenic in humans
Class 2A: Probably carcinogenic in humans

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	Activity (current status)	Evidence in humans (cancer sites)	Evidence in animals	Mechanistic evidence	Classification*
Tetrachloro- <i>p</i> -phos	Insecticide (restricted in the EU and for most uses in the USA)	Inadequate	Sufficient	-	2B
Parathion	Insecticide (restricted in the USA and EU)	Inadequate	Sufficient	-	2B
Malathion	Insecticide (currently used; high production volume chemical)	Limited (non-Hodgkin lymphoma, prostate)	Sufficient	Genotoxicity, oxidative stress, inflammation, receptor-mediated effects, and cell proliferation or death	2A†
Diazinon	Insecticide (restricted in the USA and EU)	Limited (non-Hodgkin lymphoma, leukaemia, lung)	Limited	Genotoxicity and oxidative stress	2A†
Glyphosate	Herbicide (currently used; highest global production volume herbicide)	Limited (non-Hodgkin lymphoma)	Sufficient	Genotoxicity and oxidative stress	2A†

EU-European Union. *See the International Agency for Research on Cancer (IARC) preamble for explanation of classification system (amended January, 2006). †The 2A classification of diazinon was based on limited evidence of carcinogenicity in humans and experimental animals, and strong mechanistic evidence; for malathion and glyphosate, the mechanistic evidence provided independent support of the 2A classification based on evidence of carcinogenicity in humans and experimental animals.

Table: IARC classification of some organophosphate pesticides

International Agency for Research on Cancer
World Health Organization

JNCI | Natl Cancer Inst (2018) 110(9): dx4233
doi: 10.1093/jnci/dkx233
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Article

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Glyphosate Use and Cancer Incidence in the Agricultural Health Study

Gabriella Andreotti, Stella Koutros, Jonathan N. Hofmann, Dale P. Sandler, Jay H. Lubin, Charles F. Lynch, Catherine C. Lerro, Anneclaire J. De Roos, Christine G. Parks, Michael C. Alavanja, Debra T. Silverman, Laura E. Beane Freeman

Abstract
Background: Glyphosate is the most commonly used herbicide worldwide, with both residential and agricultural uses. In 2015, the International Agency for Research on Cancer classified glyphosate as "probably carcinogenic to humans," noting strong mechanistic evidence and positive associations for non-Hodgkin lymphoma (NHL) in some epidemiologic studies. A previous evaluation in the Agricultural Health Study (AHS) with follow-up through 2003 found no statistically significant associations with glyphosate use and cancer at any site.

Methods: The AHS is a prospective cohort of licensed pesticide applicators from North Carolina and Iowa. Here, we updated the previous evaluation of glyphosate with cancer incidence from registry linkages through 2012 (North Carolina/2013 Iowa). Lifetime days and intensity-weighted lifetime days of glyphosate use were based on self-reported information from enrollment (1993-1997) and follow-up questionnaires (1999-2005). We estimated incidence rate ratios (IRRs) and 95% confidence intervals (CIs) using Poisson regression, controlling for potential confounders, including use of other pesticides. All statistical tests were two-sided.

Results: Among 54 251 applicators, 44 932 (82.8%) used glyphosate, including 7 779 incident cancer cases (17.3% of all cases). In unadjusted analyses, glyphosate was not statistically significantly associated with cancer at any site. However, among applicators in the highest exposure quartile, there was an increased risk of acute myeloid leukemia (AML) compared with never users (IRR = 1.44, 95% CI = 0.94-2.23, $P_{trend} = .10$), though this association was not statistically significant. Results for AML were similar with a five-year ($IRR_{5-year} = 2.32$, 95% CI = 0.98 to 5.51, $P_{trend} = .07$) and 20-year exposure lag ($IRR_{20-year} = 2.06$, 95% CI = 1.05 to 3.97, $P_{trend} = .04$).

Conclusions: In this large, prospective cohort study, no association was apparent between glyphosate and any solid tumors or lymphoid malignancies overall, including NHL and its subtypes. There was some evidence of increased risk of AML among the highest exposed group that requires confirmation.

Een hormoonverstorende stof (Endocrine disruptor)

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...verstoort **aanmaak** van natuurlijke hormonen
en/of

..verstoort **transport** van natuurlijke hormonen
en/of

..verstoort **werking** van natuurlijke hormonen

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Attention-Deficit-Hyperactivity Disorder and Urinary Metabolites of Organophosphate Pesticides
Maryse F. Bouchard, David A. Bellinger, Robert O. Wright, and Marc G. Weiskopf
Pediatrics 2010;125:e1270. originally published online May 17, 2010; DOI: 10.1542/peds.2009.3058

Fetal Organophosphate Metabolite and Organochlorine Levels and Performance on the Bayley Neonatal Behavioral Assessment Scale in a Multietnic Pregnancy Cohort
Stephanie M. Engel¹, Gertrud S. Berkowitz¹, Dana B. Barr², Susan L. Teitelbaum¹, Jodi Siskind¹, Stefanie J. Meisel¹, James G. Wehnur¹, and Mary S. Wolff¹

Concentraties OP-pesticiden in NL 2000-2010

Table 6. Lost IQ points and associated socio-economic cost per year of OPs exposure for three exposure groups in the Netherlands. Calculations are based on the ERR from the CHAMACOS -study cohort (Bouchard et al., 2011)

Exposure group	Total DAP reference level (nmol/L)	IQ loss per newborn (95% C.I.)	Amount of new-borns
P50-P75	272	1.69 (-2.72; -0.66)	42 835
P75-P95	494	-3.14 (-5.04; -1.23)	34 268
>P95	1116	-5.12 (-8.23; -2.01)	8567
Total			

What are the socio-economic cost for the NL?

Table 6. Lost IQ points and associated socio-economic cost per year of OPs exposure for three exposure groups in the Netherlands. Calculations are based on the ERR from the CHAMACOS -study cohort (Bouchard et al., 2011)

Exposure group	Total DAP reference level (nmol/L)	IQ loss per newborn (95% C.I.)	Amount of new-borns	IQ loss per exposure group	Socio-economic cost (95% C.I.) (million € / year of exposure)
P50-P75	272	-1.69 (-2.72; -0.66)	42 835	(-116 070; -29 393)	-875 (-1407; -344)
P75-P95	494	-3.14 (-5.04; -1.23)	34 268	(-107 466; -172 713; -42 215)	-1303 (-2093; -512)
>P95	1116	-5.12 (-8.23; -2.01)	8567	(-43 856; -70 483; -17229)	-532 (-854; -209)
Total				-223 455 (-359 266; -87 821)	-2709 (-4354; -1064)

1 - 4 miljard € per jaar

Table 9. Range of EDC-attributable cost per health effect and total EDC-attributable socio-economic cost the EU (in billion €). Outliers in cost estimates and their proposed alternatives are indicated in red.

Source	Basic Council	REAL	Thousands	This /other reports	overall range	Proposed for best range								
etiological fraction / type of estimate	2%	20%	80%	Total (%)	low	base case	high	1% / low	2.5% / base case	10% / high	lowest	highest	lowest	highest
Reproductive tract and fertility														
Reduced male fertility			0,048 - 0,063	0,120 - 0,135							0,007	4,75	0,007	0,120
Cryptorchidism	0,007	0,072	0,143		-11	4,75	-11				0,018	0,303	0,018	0,303
Hypogonadism	0,009	0,089	0,178		0,018 - 0,029	0,045 - 0,065	0,117	0,130	-11		0,009	0,178	0,009	0,178
Endometriosis								0,773	1,94	7,75	0,773	7,75	0,773	7,75
Neurobehavioral diseases and disorders														
Autism spectrum disorders (ASD)			4,32	13,3	0,080	0,199	0,399				0,080	13,3	0,080	13,3
AD/HD			0,014	0,015		2,62	4,14	4,93			0,014	4,93	1,22	4,93
KJ loss					42,2	133,4	183,6	32,8	84,3	136	42,2	183,6	42,2	183,6
Intellectual retardation					6,11	22,6	35,43				6,11	35,4	6,11	35,4
Neural tube defects								0,008	0,019	0,077	0,008	0,077	0,008	0,077
Neuroendocrine-related cancers														
Breast cancer			0,020	0,050							0,020	0,050	0,020	0,050
Prostate cancer			0,000	0,000							0,000	0,000	0,000	0,000
Health (reproductive germ cell metabolic syndrome, knee Obesity: (20														
Diabetes mellitus (Type 2)								0,175	0,612	1,78	0,175	1,78	0,175	1,78
Alzheimer														
TOTALs (billion €) after correction	0,019	0,381	1,185	12,7	33,8	44,7	182,6	270,6	NA	NA	68,9	292,6	56,4	289,9
TOTALs (billion €) after correction	NA	NA	NA	NA	152	NA	NA	NA	NA	NA	NA	NA	NA	NA
(95% C.I. 93 - 212)														

Geschatte directe en indirecte kosten ED effects, including biociden, 50-300 miljard € op jaarbasis voor EU28 (waarvan >50% gedrags en hersenafwijkingen)

Rijk, L., van Duursen M., & van den Berg, M. (2016) Health effects related to Endocrine Disrupting Chemicals and their socio-economic impact in the EU -An inventory, evaluation and way forward in cost estimates of EDC-related health effects (in prep). The Netherlands: Institute for Risk Assessment Sciences (IRAS), Utrecht University.



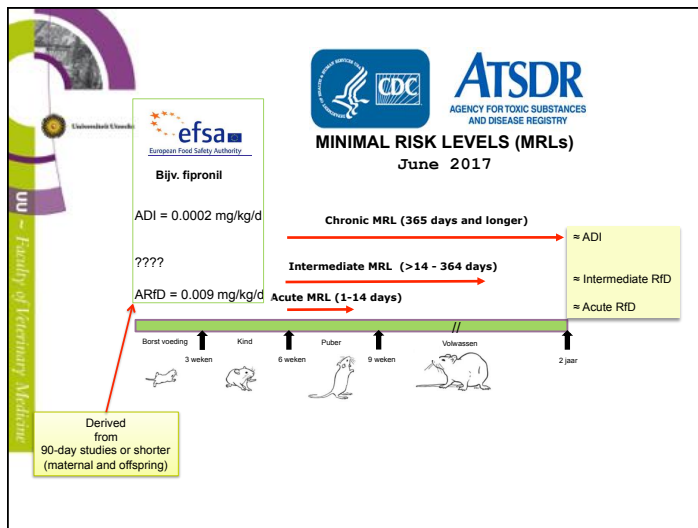
Tabel 3: Controlegegevens per land van herkomst (op alfabetische volgorde)

Land	aantal monsters	% boven wettelijke norm	middelen per monster
Argentinië	62	3,2	2,8
België	60	3,3	2,3
Brazilië	231	7,8	2,4
China	154	1,3	2,8
Colombia	776	6,4	3,3
Costa Rica	76	11,8	2,0
Cuba	80	1,3	1,4
Dominicaanse Republiek	188	15,4	1,7
Duitsland	45	0,0	1,6
Egypte	455	10,3	3,4
Frankrijk	63	1,6	1,1
India	187	8,6	4,2
Israël	---	---	---
Italië	---	---	---
Kenya	---	---	---
Marokko	---	---	---
Mexico	---	---	---
Nederland	---	---	---
Onbekend	---	---	---
Peru	---	---	---
Spanje	---	---	---
Suriname	---	---	---
Thailand	139	17,3	1,4
Turkije	80	7,8	3,3
Verenigde Staten	48	2,1	1,6
Vietnam	100	30,0	2,4
Zuid-Afrika	353	3,7	---
Gesamenste landen	7962	5,4	---
Totaal	8389	5,7	---

Biociden op groente en fruit : Een Risico?

- Meeste overschrijdingen van buiten de EU (ca 3%)
- Eenmalige overschrijding in voedsel minimaal risico
- Risico zit in chronische overschrijding
- Kwetsbaarste groepen zwangere vrouwen, kinderen

Nederlandse Voedsel- en Warenautoriteit
Ministerie van Economische Zaken



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Biociden op groente en fruit : Een Risico?

- Biologische producten geen meerwaarde voor algemene volksgezondheid (perceptie) vanuit biociden oogpunt?

Nederlandse Voedsel- en Warenautoriteit
Ministerie van Economische Zaken

JAMA Internal Medicine | Original Investigation

Association Between Pesticide Residue Intake From Consumption of Fruits and Vegetables and Pregnancy Outcomes Among Women Undergoing Infertility Treatment With Assisted Reproductive Technology

Yu-Hsin Chen, MD, ScD, Paige L. Williams, PhD, Matthew R. Utzinger, MS, MEd, Ashley J. Galanis, ScD, Lisa M. Engelke, PhD, Yusef D. Al-Sayid, MD, Thomas L. Whit, MD, Jennifer A. Cook, MD, Ross Haines, MD, ScD, Jorge E. Chavarro, MD, ScD, for the ART+Study Team

IMPORTANCE: Animal experiments suggest that ingestion of pesticide residues at environmentally relevant concentrations decreases the number of live-born offspring. Whether the same is true in humans is unknown.

OBJECTIVE: To examine the association of preconception intake of pesticide residues in fruits and vegetables (FVs) with outcomes of infertility treatment with assisted reproductive technologies (ART).

DESIGN, SETTING, AND PARTICIPANTS: The analysis included 225 women who completed a diet assessment and subsequently underwent 541 ART cycles in the Environment and Reproductive Health (EARTH) prospective cohort study (2007-2008) at a fertility center at a teaching hospital. We categorized FVs as having high or low pesticide residues using a validated method based on surveillance data from the US Department of Agriculture. Cluster-weighted generalized estimating equations were used to analyze associations of high- and low-pesticide-residue FV intake with ART outcomes.

MAIN RESULTS AND RELEVANCE: Adjusted probabilities of clinical pregnancy and live birth per treatment cycle.

RESULTS: In the 225 participants (mean [SD] age, 35.1 [4.0] y; body mass index, 24.1 [4.3], mean [SD] intake of high- and low-pesticide-residue FVs were 17.0 (5.0) and 2.8 (1.0) servings/d, respectively. Greater intake of high-pesticide-residue FVs was associated with a lower probability of clinical pregnancy and live birth. Compared with women in the lowest quartile of high-pesticide FV intake (0 servings/d), women in the highest quartile (2-2.3 servings/d) had 18% (95% CI, 1%-30%) lower probability of clinical pregnancy and 26% (95% CI, 13%-37%) lower probability of live birth. Intake of low-pesticide-residue FVs was not significantly related to ART outcomes.

CONCLUSIONS AND RELEVANCE: Higher consumption of high-pesticide-residue FVs was associated with lower probabilities of pregnancy and live birth following infertility treatment with ART. These data suggest that dietary pesticide exposure within the range of typical human exposure may be associated with adverse reproductive consequences.

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• Mengsel effecten:

- *Regelmatig 5-10 verschillende biociden groente en fruit*
- *Additiviteit voor biociden met zelfde werkingsmechanismen, maar bereiken gezamenlijke drempelwaarde of ADI bij normaal consumptie zeldzaam*
- *Additiviteit in milieu (bijv. non target species) zeker relevant bij biociden met zelfde werkingsmechanisme door hogere concentraties*
- *Synergisme in de praktijk zeer zeldzaam*
- *Niet additief combinatie effect biociden met verschillend werkingsmechanisme wel milieu-relevant bij overschrijding drempelwaarde van individuele stoffen*

Ecologische risico's van biociden?





European Academies easac Science Advisory Council

Ecosystem services, agriculture and neonicotinoids

1. There is an increasing body of evidence that the widespread prophylactic use of neonicotinoids has severe negative effects on non-target organisms that provide ecosystem services including pollination and natural pest control.

4. Widespread use of neonicotinoids (as well as other pesticides) constrains the potential for restoring biodiversity in farmland under the EU's Agri-environment Regulation.



EASAC policy report 26
April 2015
ISBN: 978-3-8547-3437-1
This report can be found at www.easac.eu

building science into EU policy

“Risico-Voordeel” analyses van biociden in mondiaal perspectief

World Health Organization

FAO
FIAT PARS

Flies

Mosquito

- Chikungunya
- Dengue
- Rift Valley fever
- Yellow fever
- Zika
- Malaria
- Japanese encephalitis
- Lymphatic filariasis
- West Nile virus

World Health Organization

Every year more than 1 billion cases and over 1 million deaths from vector-borne diseases such as malaria, dengue, schistosomiasis, human African trypanosomiasis, leishmaniasis, Chagas disease, yellow fever, Japanese encephalitis and onchocerciasis, globally.

Vector-borne diseases account for over 17% of all infectious diseases.

Triatomine bugs
Chagas disease

In Nederland en EU landen de “luxe” om ons te bekommeren over eco-effecten. Grootste deel wereldbevolking heeft deze “luxe” niet door voedselschaarste, natuurrampen, klimaat etc.

Rijke landen (w.o. NL) voortouw nemen in ontwikkeling ecologisch en ecotoxicologisch verantwoorde landbouw productie-methoden, die uiteindelijk ook toepasbaar zijn in andere delen van de wereld

Maken wij ons terecht zorgen over het gebruik van bestrijdingsmiddelen?

- **Kanker**
 - **Ne**. Genotoxisch biociden niet in voedsel, alleen met biociden met drempelwaarde en vaak proefdier specifiek
- **Endocriene effecten**
 - Mens: **Onzekerheid** over effecten voornamelijk in vroege levensfase voor moderne biociden (insect specifiek, snelle afbraak door metabolisme)
 - Milieu: **Ja**, te hoge milieu-concentraties en aantoonbare effecten op “non-target” soorten
- **ADI of Acute/Intermediaire Referentie Waarde?**
 - Gebruik **ADI** leidt meestal tot **overschatting risico** (tijdsduur, veiligheidsmarge)
 - **Acute/Intermediaire Referentie Waarde** is vaak meer **realistisch** voor risicoschatting bij incidentele overschrijding



Bedankt voor uw aandacht

VRAGEN?