Fit to Drive

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Meta-analysis on the effects of psychoactive substances on driving

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- Meta-analysis of alcohol (Deliverable 1.1.2a)
- Meta-analysis of medicines and illegal drugs (Deliverable 1.1.2b)

  - Antipsychotics
  - Anxiolytics
  - Hypnotics and sedatives
  - Antidepressants
  - Antihistamines
  - Amphetamines
  - Cocaine
  - Cannabis

➢ Results of meta-analysis of alcohol serve as reference base for other substances

Literature selection

- Collection of experimental studies (1954-2009) concerning
  - the effects of alcohol, medicines and illegal drugs on
    - driving-related performance
    - social behaviour
    - mood
  - pharmacokinetics of illegal drugs and medicines

➢ Alcohol: From over 12,000 references, 450 studies were selected with a total of 5,300 findings referring to different BAC levels and tests

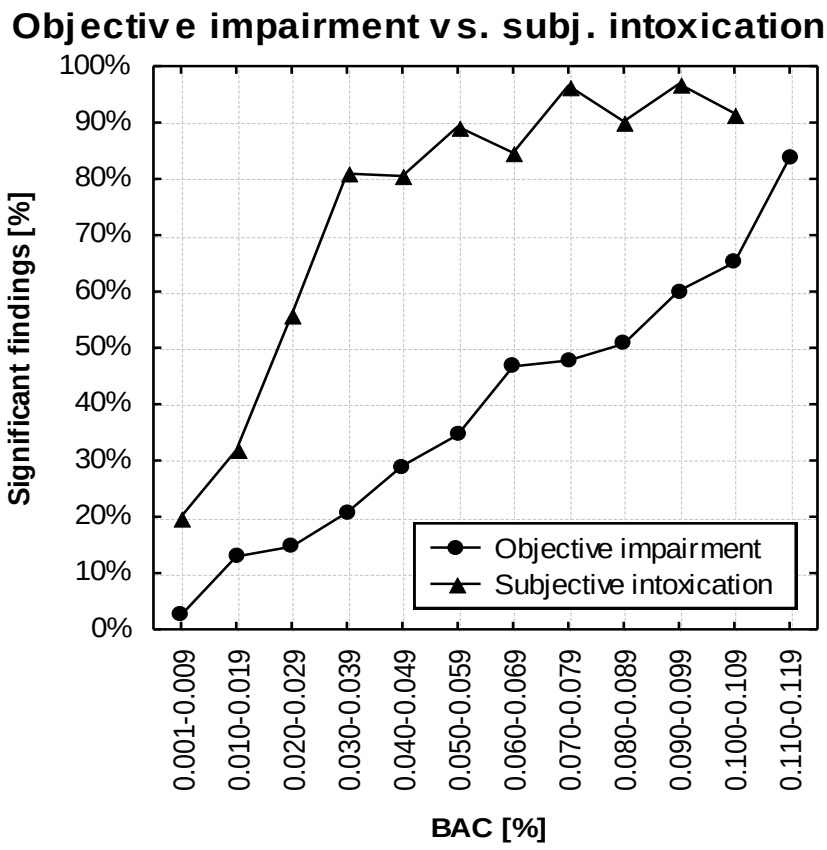
➢ Medicines and illegal drugs: From over 20,000 references, 718 studies (considering 33 different agents) were selected with a total of 19,271 findings referring to different doses / concentrations and tests

- Classification of assessed behaviour according to driving-related categories:
  - Visual functions
  - Attention
  - Divided attention
  - En-/decoding (information processing and memory)
  - Reaction time
  - Psychomotor skills
  - Tracking
  - Driving
  - Social behaviour (e.g. aggression)
  - Mood (e.g. drowsiness)

- Impairment is assumed, if a substance effect reaches a significance level of at least 5%
- The significant alcohol findings are summarised for the same BAC groups (in 0.01% steps)
- For each BAC group the percentage of significant effects is determined, leading to an impairment function

- Meta-analytic approach of medicines/illegal drugs has to be restricted to studies with
  - single oral administration
  - in healthy subjects
  - < 60 years
- Calculation of the substance concentration for the testing time based on the evaluation of pharmacokinetic studies
- Time-dependent and concentration-dependent approximation of the empirical data (calculation of new parameters is possible)

Short summary of results concerning alcohol



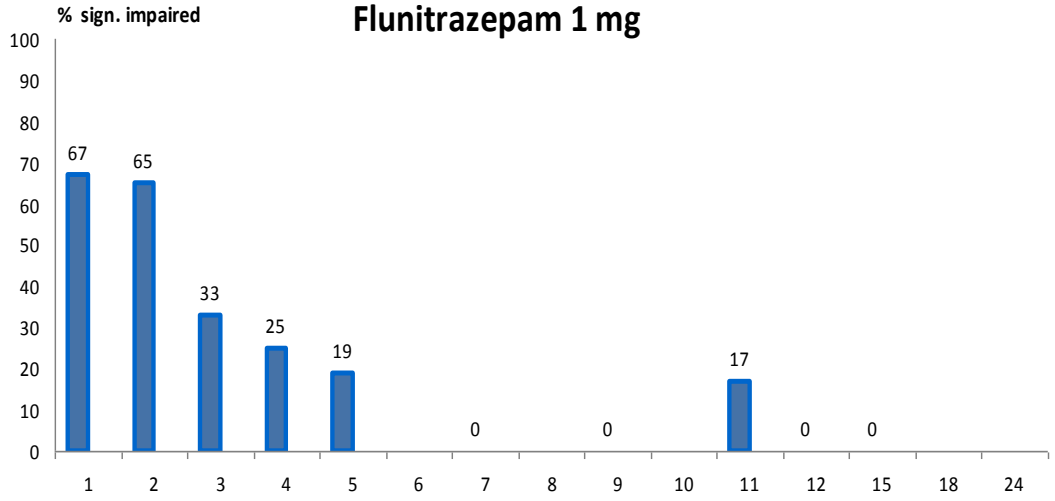
Percentage of impaired findings with 0.040-0.059% BAC:

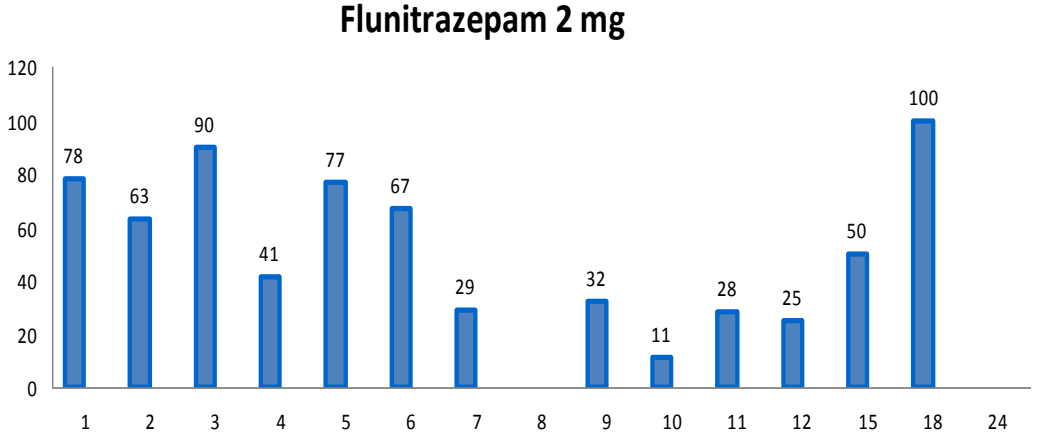
Behavioural categories	%
Subjective intoxication	86%
Driving	48%
Tracking	46%
Psychomotor skills	38%
Subjective fatigue	33%
Visual functions	33%
Reaction time	29%
En-/Decoding	27%
Aggression	27%
Attention	24%
Divided attention	20%
Mean objective impairment	32%

Results concerning medicines: Dose- and time-dependant performance

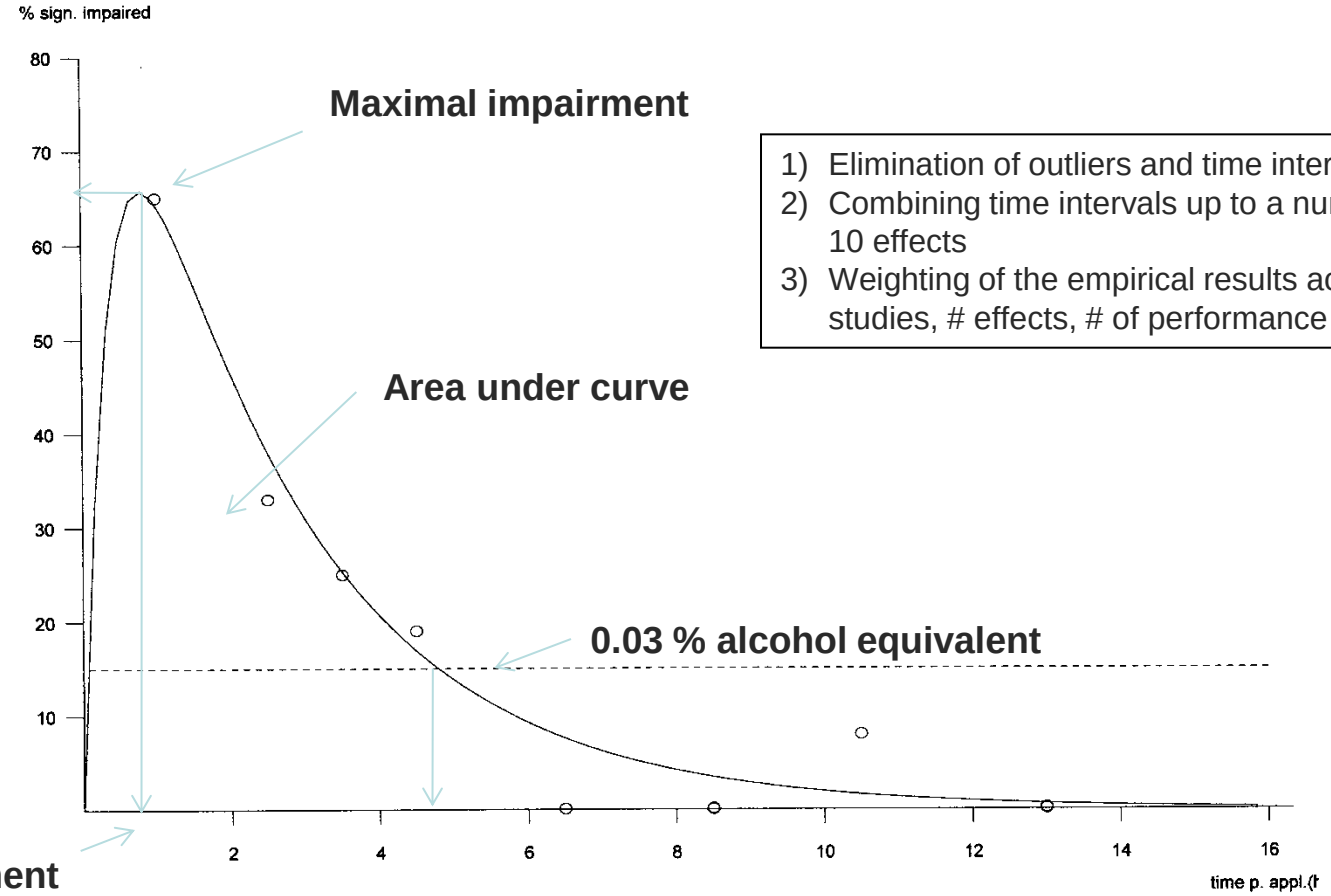
Example Flunitrazepam:

- Basis for the evaluation:
  29 studies with 491 findings
- Two main doses:
  1 mg and 2 mg



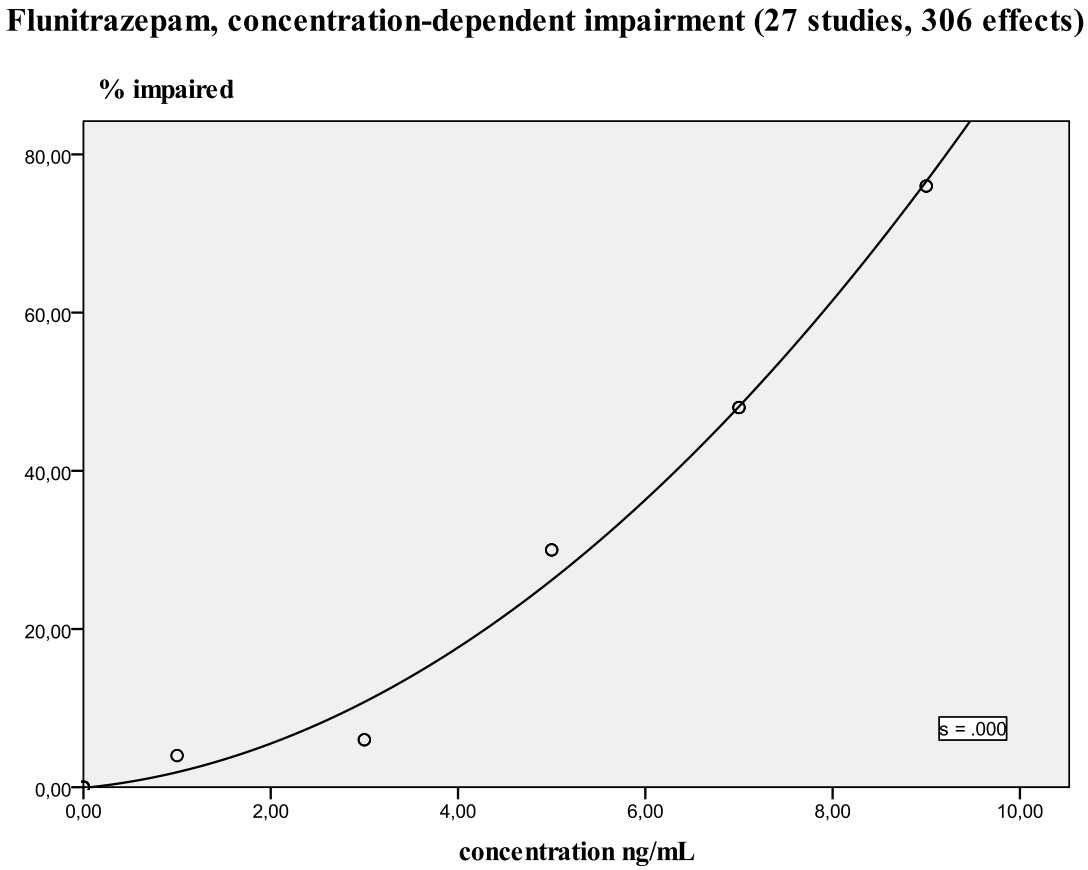


Flunitrazepam 1 mg: Time-dependant impairment with curve fitting



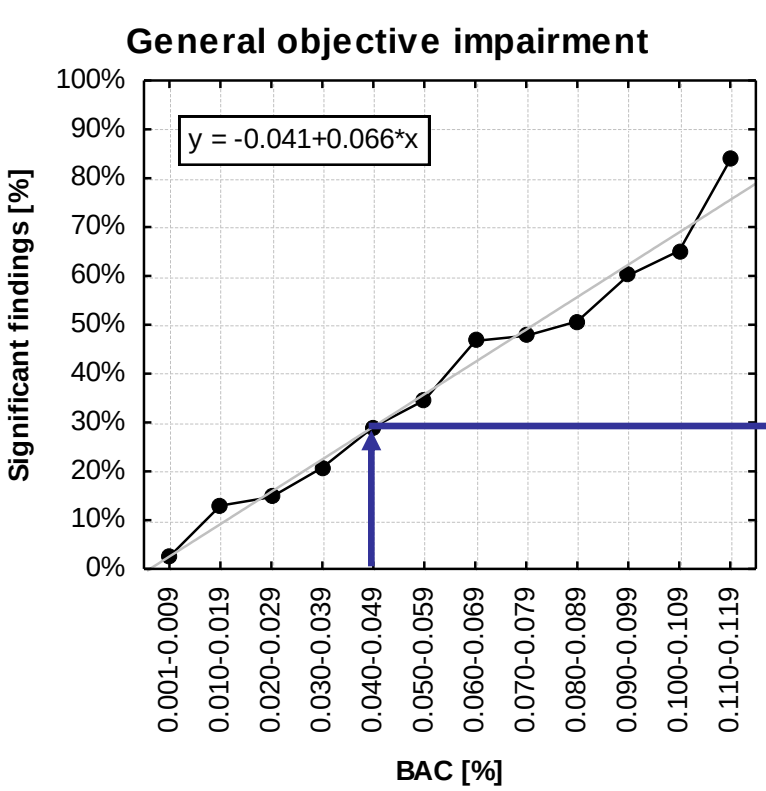
1) Elimination of outliers and time intervals >18 hours
2) Combining time intervals up to a number of at least 10 effects
3) Weighting of the empirical results according to # studies, # effects, # of performance areas

Flunitrazepam 1 mg: Concentration-dependant impairment with curve fitting

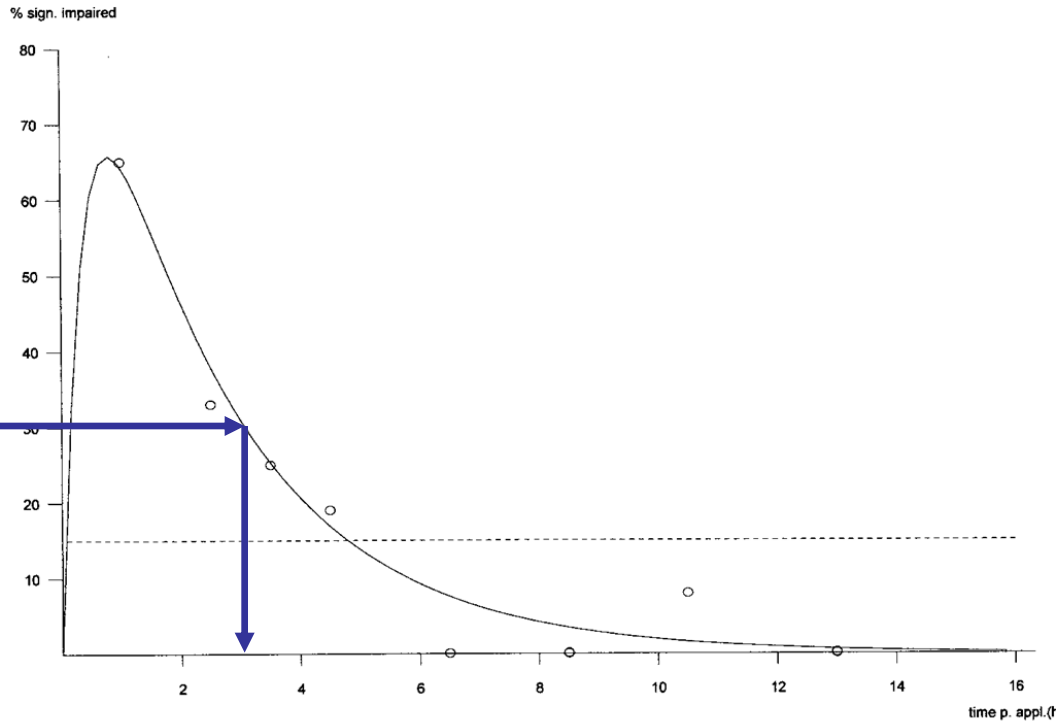


Comparison with alcohol via percentage of sign. impaired findings

Alcohol



Flunitrazepam 1 mg



Flunitrazepam: Overview of results

Agent	Flunitrazepam	
Number of studies	29	
Number of effects	491	
Checked doses (mg)	0.5 - 4.0	
Tabularly evaluable doses (mg) No. Studies/no. effects	1 16/165	2 11/176
Max. sign. impaired test results (%)	66 (60 - 98)	92 (81 - 100)
Time until maximum impairment (h)	0.75 (0.50 - 1.0)	2.25 (2.0 - 2.25)
Alcohol equivalence of max. imp. (%)	>0.08	>0.08
Duration until < 15% impairment (h)	5.0 (3.75 - 7.75)	14.0 (12.75 - 15.25)
Degree of impairment (AUC)	115 (85 - 177)	461 (374 - 562)
0.05% alcohol equivalent (ng/ml) Recommended dose (mg) % of max. recommended dose (mg)	5.4 (5.0 - 5.8) 0.5 - 1 70 of 1 mg (65 - 75)	

No meta-analytical approach possible for:

- Studies with multiple administrations to healthy subjects
  - Too few studies per agent
  - Heterogeneity of the studies with respect to test design (dose, frequency, period of time of administration…)
- Studies with patients
  - Too few studies per disease
  - Heterogeneity of the studies with respect to intensity of disease, patients, medical therapy, control group…

➢ All data were related to single applications to healthy subjects

➢ Depiction of „worst case“, comparable to recreational use

Conclusions

- Establishment of time-/dose-dependent and concentration-dependent profiles for 33 relevant psychoactive substances
- Possibility of recommendations on intensity and duration etc. of performance impairment
- Comparison with equivalent concentrations of alcohol
- Reality: traffic-related “danger” of a medicament depends on more influencing variables than only on performance impairment

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