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Descriptive analytical data and consequences for calculation of common reference intervals in the Nordic Reference Interval Project 2000

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In the Nordic Reference Interval Project (NORIP), data from 102 Nordic clinical chemical laboratories were obtained. Each laboratory reported analytical data on up to 25 of the most commonly used clinical biochemical properties, including results from each of a minimum of 25 reference individuals. A reference material consisting of a liquid frozen pool of serum with values traceable to reference methods (used as the project "calibrator" for non-enzymes to correct reference values) was measured together with other serum pool controls in each laboratory in the same analytical series as the project samples. The data on the controls were used to evaluate the analytical quality of the routine methods. For reference interval calculations, only such reference values on enzymes were accepted that were obtained by applying the International Federation of Clinical Chemistry (IFCC) compatible methods (37°C), while "calibrator"-corrected reference values were used in the cases of non-enzymes. For each property, gender- and age-specific reference intervals were estimated, based on simple non-parametric calculations and using objective criteria to perform partitioning into subgroups. It is concluded that the same reference intervals are applicable in all five Nordic countries. The following descriptive data for the considered properties are presented in the tables: number of measurement values from each country and measurement system, certified/indicative target values for controls, differences between methods and measurement systems together with coefficients of variation, effects of control correction on the measurement values, differences between subgroups as determined by age, gender, country and material, and comparison of the new reference intervals with those presented in standard textbooks. The 25 components involved in this project were (listed in alphabetical order): Alanine transaminase, albumin, alkaline phosphatase, amylase, amylase pancreatic type, aspartate transaminase, bilirubin, calcium, carbamide, cholesterol, creatine kinase, creatininium, γ-glutamyltransferase, glucose, HDL-cholesterol, iron, iron-binding capacity, lactate dehydrogenase, magnesium, phosphate, potassium, protein, sodium, triglyceride and urate.

Key words: Analytical validation; reference limit; reference value

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INTRODUCTION

The main objective of the Nordic Reference Interval Project (NORIP) [1–2] was to establish common Nordic reference intervals for 25 clinical biochemical properties frequently measured in serum and plasma. Recruitment of reference individuals, collection of samples, and the laboratory analyses of these were accomplished in each of 102 Nordic medical laboratories according to a common protocol [3]. Post-analytical treatment of data, including calculation of the new reference intervals, was performed centrally. A brief description of this project and its main results are available elsewhere [1]. In the present report, we focus on descriptive analytical data, which are relevant for calculation of reference intervals in particular. Some of these data will also be useful for evaluation of local methods as expected from those Nordic clinical chemical laboratories that intend to introduce the new reference intervals. For more detailed data, probably needed for the latter purpose, readers are referred to the home site of the project [2]. Together with tables presenting gender- and age-specific reference intervals for adults in the Nordic countries, a considerable amount of other useful information obtained in this project, such as comparisons between plasma and serum, both fresh and thawed, will be documented. Enzymes will be considered by Strømme *et al.* in another project publication [4] and will not be discussed in detail in the present report. Some data also on enzymes may be shown in our tables, however, if considered appropriate.

Terminology

Clinical biochemical properties. Naming of the properties involved in this project follows the terminology used in the NPU code system. The names in that system are composed of designations for the material (*in vivo*), the component, and the measured quantity, following certain syntactic and semantic rules (http://www.labinfo.dk/English/Documents/syntax.htm#systdef) [5]. The abbreviations used in the present report are given in the first column of Table I. Because this coding system refers to quantities *in vivo*, the "P–" before the names of components in Table I represents plasma *in vivo*. The actual measured specimen could be of serum or plasma (stabilized with Li-heparin), and both of these could be fresh or thawed. The listed abbreviations will also be used for the corresponding properties in control sera, and they could also refer to the component in general. The kind of use being implemented in a particular case should be evident from the context. Note that the NPU code specifies the unit. The NPU coding system includes special codes for properties as measured by using certain methods (there are such codes, e.g., for creatininium as determined by the Jaffé methods and other special codes for that property when enzymatic methods are used), and for glucose and triglyceride there are special codes for fasting. However, in this report the general codes and names are used.

Reference samples and materials. To avoid confusion between the concept of "reference sample" (a sample from a reference individual) and that of "reference material", "control" will be used for the latter one.

Standard units. Some of the properties were expressed in varying units by the participating laboratories. In such cases, the most frequently used unit was selected as the standard unit, and the data expressed in other units were converted to that unit by using appropriate multiplying factors. All units deviating from the standard unit are presented in Table II together with the respective conversion factors.

MATERIALS, METHODS AND RESULTS

Statistics

General statistical calculations were done with the Microsoft® Access and Microsoft® Excel programs and calculations of reference intervals with the RefVal 4.0 program [6]. Partitioning into subgroups was assessed using recently suggested proportion criteria [7] as implemented in a project-specific, modified version of RefVal 4.0.

NORIP concept

The participating laboratories received the following controls on dry ice: CAL, X, P, LOW

TABLE I. Nomenclature and codes for the properties involved in NORIP. The properties are listed in alphabetic order as determined by their abbreviations.

Abbreviation	International name	Unit	NPU code
Albumin	P – albumin; mass c.(proc.)	g/L	DNK05001*
ALP	P – alkaline phosphatase; cat.c.(IFCC 1998)	U/L	NPU19655
ALT	P – alanine transaminase; cat.c.(IFCC 1998)	U/L	NPU19651
AMY	P – amylase; cat.c.(IFCC 1998)	U/L	NPU19652
AMY-P	P – amylase, pancreatic type; cat.c.(IFCC 1998)	U/L	NPU19653
AST	P – aspartate transaminase; cat.c.(IFCC 1998	U/L	NPU19654
Bilirubin	P – bilirubins; subst.c.	μmol/L	NPU01370
Calcium	P – calcium(II); subst.c.	mmol/L	NPU01443
Calcium, corr.	P – calcium(II); subst.c.(corr.; proc.)[1]	mmol/L	NPU04169
Carbamide	P – carbamide; subst.c.[2]	mmol/L	NPU01459
Cholesterol	P – cholesterol + ester; subst.c.	mmol/L	NPU01566
CK	P – creatine kinase; cat.c.(IFCC 1998)	U/L	NPU19656
Creatininium	P – creatininium; subst.c.	μmol/L	NPU18016
Glucose	P – glucose; subst.c.	mmol/L	NPU02192
GT	P – γ-glutamyltransferase; cat.c.(IFCC 1998)	U/L	NPU19657
HDL-chol.	P – cholesterol + ester, in HDL; subst.c.	mmol/L	NPU01567
Iron	P – iron; subst.c.	μmol/L	NPU02508
LD	P – lactate dehydrogenase; cat.c.(IFCC 1998)	U/L	NPU19658
LDL-chol.	P – cholesterol + ester, in LDL; subst.c.[3]	mmol/L	NPU01568
Magnesium	P – magnesium(II); subst.c.	mmol/L	NPU02647
Phosphate	P – phosphate(P; inorganic); subst.c.	mmol/L	NPU03096
Potassium	P – potassium ion; subst.c.	mmol/L	NPU03230
Protein	P – protein; mass c.	g/L	NPU03278
Sodium	P – sodium ion; subst.c.	mmol/L	NPU03429
TIBC	P – iron binding capacity; subst.c.[4]	μmol/L	NPU04133
Iron sat.	Transferrin (Fe-binding sites; P – Iron; subst.fr.[5]		NPU04191
Triglyceride	P – triglyceride; subst.c.	mmol/L	NPU04094
Urate	P – urate; subst.c.	μmol/L	NPU09356

Calcium, corr = calcium + 0.020·(41.3 – albumin).
Carbamide = Urea.
LDL-chol. = cholesterol – HDL-chol. – triglyceride/2, where triglyceride < 4 mmol/L.
TIBC could be calculated as twice the concentration of transferrin in μmol/L.
Iron sat = iron/TIBC (in units shown above).
*Danish code

and HIGH. These controls were measured together with the project samples and are specified in detail elsewhere [1, 7]. As a minimum contribution to the project, the laboratories were asked to perform measurements on these controls and on thawed serum samples collected from each reference individual, together with thawed plasma samples collected from 10% of them, and all of these measurements were expected to be made in one series. Because many laboratories made measurements also on fresh samples, there may be measurement results on both thawed and fresh materials (serum and Li-heparin plasma) for a particular reference individual and property. The total numbers of reference and control values obtained from each country are presented in Table III.

The number of reference values obtained from each country for thawed serum is shown in Table IV for each property.

TABLE II. Factors used to convert locally applied units to those selected as standard ones for NORIP.

Property	Local unit		Unit factor		Standard unit
Enzymes	μkat/L	×	60	=	U/L
Albumin	μmol/L	×	0.0665	=	g/L
TIBC	g/L	×	25.1	=	μmol/L
Urate	mmol/L	×	1000	=	μmol/L

NORIP = Nordic Reference Interval Project; TIBC = total iron-binding capacity.

Comment. Overall, about 30% of the measurements on thawed serum come from each of

TABLE III. Numbers of reference and control values from each country in the NORIP database.

Country	Reference values	Control values	Sum
Denmark	19 337	14 163	33 500
Finland	52 808	27 139	79 947
Iceland	1959	506	2465
Norway	27 439	15 844	43 283
Sweden	23 201	15 714	38 915
Sum	124 744	73 366	198 110

Finland and Norway, about 20% from each of Denmark and Sweden, and about 3% from Iceland. However, the distributions are quite different from this general pattern in some cases. Sweden and Norway contributed by 60% and 21%, respectively, to the data of AMY-P. For protein, the contribution of Sweden was only 7%, while Finland and Norway supplied 35% and 40%, respectively, of those data. For total iron-binding capacity (TIBC), the contributions of Norway and Sweden were 57% and 27%, respectively.

Elimination of errors from submitted data

A considerable effort was made to eliminate errors from the submitted data. The laboratories were recommended to check these before submission. Afterwards, each laboratory received a report with descriptive statistics on their data, including the mean, the standard deviation and the number of control data for each property, and a comparison with the respective target value. It appeared that many laboratories had not checked their data appropriately before submission.

Methods and instruments

The analytical method used for each measured property in each laboratory was characterized by the following parameters: method group, method name, instrument group (manufacturer), instrument name, unit, slope (S) and intercept (I) (cf. "Intercept and Slope" below). The first four of these parameter values were filled in following the classification used in

TABLE IV. Numbers of reference values obtained for thawed serum and their distributions by countries for each property.

Property	Serum, thawed	Denmark	Finland	Iceland	Norway	Sweden
Albumin	2819	19%	27%	3%	31%	20%
ALP	2477	20%	26%	3%	29%	22%
ALT	2754	19%	26%	3%	31%	21%
AMY	2021	20%	32%	4%	36%	9%
AMY-P	850	12%	7%		21%	60%
AST	2452	10%	29%	3%	35%	23%
Bilirubin	2818	19%	27%	3%	31%	20%
Calcium	2703	17%	28%	3%	31%	21%
Carbamide	2584	21%	25%	3%	31%	20%
Cholesterol	2766	19%	28%	3%	30%	20%
CK	2641	20%	27%	3%	33%	17%
Creatininium	2709	20%	28%		31%	21%
Glucose	2358	13%	28%	4%	34%	21%
GT	2557	15%	27%	3%	33%	22%
HDL-chol.	2637	18%	29%	3%	30%	20%
Iron	2370	17%	27%	4%	31%	22%
LD	2376	21%	27%	4%	27%	22%
Magnesium	2198	22%	22%	4%	31%	21%
Phosphate	2656	20%	27%	3%	30%	20%
Potassium	2757	19%	28%	3%	30%	21%
Protein	2097	14%	35%	4%	40%	7%
Sodium	2763	18%	28%	3%	30%	21%
TIBC	942	6%		9%	57%	27%
Triglyceride	2714	18%	28%	3%	30%	21%
Urate	2708	19%	26%	3%	31%	21%

ALP = alkaline phosphatase; ALT = aspartate transaminase; AMY = amylase; AMY–P = amylase-pancreatic type; AST = aspartate transaminase; CK = creatine kinase; GT = γ-glutamyltransferase; LD = lactate dehydrogenase; TIBC = total iron-binding capacity.

TABLE V. Distributions in each country of manufacturers of instrument for measurement of potassium in thawed serum.

Instrument manufacturer	Sum	Denmark	Finland	Iceland	Norway	Sweden
Bayer, Technicon	7	2			3	2
Coulter, Beckman	8		2		2	4
Dade Behring (du Pont)	2	2				
Konelab	7		7			
Olympus	2	2				
Ortho, Vitros	23	4	2	1	12	4
Roche, Cobas	25	8	12		3	2
Roche, Hitachi	29	3	3		11	12

the method database of Labquality, a Finnish organization for external quality assessment, from the year 2000. For example, Table V shows the distributions of instrument manufacturers in each country for measurement of potassium in thawed serum.

Comments. The instrument manufacturer used by the largest number of participating laboratories in this project was Roche (52%), represented by the instrument groups of Cobas (24%) and Hitachi (including Modular) (28%). Ortho with the Vitros instruments was another widely represented manufacturer (22%). The rest of the manufacturers, used together by about 25% of the laboratories, were Bayer, Beckman and Konelab (7–8% each), and Olympus (2 laboratories). Ortho was mainly used in Norway (over 50% of all), Cobas mainly in Finland and Denmark, while the Hitachi instruments were found most frequently in Sweden and Norway. Konelab was used only in Finland. The remaining instruments were few and had similar distributions. That the distributions of instrument types vary from country to country may explain some of the differences between country-specific reference intervals, discussed later (Table XIII). In the cases of non-enzymes, the correction made by using a common calibrator with normal serum matrix should help to eliminate this problem, however (cf. below).

Modifications made to measurement values

Random number addition. A problem encountered frequently when combining reference values from many laboratories is diversity of both units and numbers of decimals in submitted measurement values. To account for the resulting differences in rounding off uncertainty, a random number between v-LSD/2 and v+LSD/2 was substituted for each reference value v, where the LSD (least significant digit) for that value is defined as $LSD = 10^{-d}$, where d is the number of decimals in v. To illustrate, if a value of 2.6 μkat/L was received and all the values from that laboratory were reported with one decimal (i.e. $LSD = 10^{-1} = 0.1$), a random number generated from a uniform distribution between 2.55 and 2.65 was substituted for 2.6. This example also shows that the uncertainty introduced by rounding off decimals to reference values for enzymes expressed in μkat/L (as is done in Sweden, mostly with one decimal, while the rest of Scandinavia uses U/L with no decimals) is $0.1\ \mu kat/L \times 60 = 6$ U/L as converted to U/L (Table II), whereas the uncertainty is only 1 U/L in the other countries.

Correction based on CAL. CAL was used as the project "calibrator" for non-enzymes, which means that all reference values were multiplied by the factor T/M, where T is the target value for CAL and M is the mean of measurements for CAL in the series where the project samples obtained from reference individuals were measured. This adjustment is called "correction" in the present report. Observe that the unit in which the reference values are expressed does not affect the factor T/M.

Intercept and slope. For enzymes [4], no similar correction was made. Instead, all reference values were calculated back to original instrument values by applying the slopes (S) and the intercepts (I) reported by the laboratory. These are constants used by the laboratories to modify original measurement values

according to $R = S \cdot O + I$, where O and R are the original and the modified values, respectively. No slope and intercept corrections were made for non-enzymes.

Trueness

Controls. The control materials used in this project were:

- CAL and X: fresh frozen (the storage temperature was between $-70°C$ and $-80°C$) serum pools from men [8].
- P: fresh frozen serum pool from women using contraceptive pills.
- HIGH: fresh frozen serum pool concentrated about 1.3 times by a freezing/thawing process.
- LOW:HIGH diluted $1+1$ with an aqueous solution containing sodium and calcium, which gives a theoretical ratio of 2.00 for HIGH/LOW (except for sodium and calcium).

Target values. Dependent on property, CAL has assigned target values from one of the following three sources:

1. IMEP 17, Material 1 transferred values from Nordic Trueness Project [9–10].
2. DGKC (Deutsche Gesellschaft für Klinische Chemie) 1997 reference methods [11].
3. Median of measured values from NORIP (HDL-chol. and TIBC).

Dependent on property, X has assigned target values from one of the following three sources [12] (cf. Table VI of this report):

1. IMEP 17, Material 1 transferred values from Nordic Trueness Project.
2. CAL transferred values from NORIP.
3. Mean values from NORIP.

Indicative target values for the controls P, HIGH and LOW were established from results obtained by using wet chemistry methods in NORIP. The reason for using only wet chemistry is the well-known fact that with dry chemistry (Ortho/Vitros) there are problems with diluted (and possibly also with concentrated) sera. For γ-glutamyltransferase (GT), creatine kinase (CK), alanine transaminase (ALT), and non-enzymes, CAL-transferred values were calculated as the mean of the laboratory means (M) for the quotient M(C)/M(CAL), where C is one of the control materials P, HIGH or LOW (values outside ± 4 standard deviations were eliminated as outliers). This mean value was subsequently multiplied by the target value for CAL. For enzymes (with the exception of GT, CK and ALT), the target values were calculated as the means of laboratory means of control values, eliminating laboratory means outside ± 4 standard deviations as outliers. The target values for CAL and X (including source of target value) and wet chemistry mean values for X, P, HIGH and LOW are presented in Table VI.

Comments. There should be and is good agreement between each target value of X (Xt) and the corresponding wet chemistry mean of X (Xm). The target value for creatininium was established with the isotope dilution, mass spectrometry method and is in agreement with enzyme creatininium methods. Still, the Jaffé method is most widely used in routine laboratories. For sodium, the certified reference value is traceable to a gravimetrical method used for establishing reference method value on IMEP 17 Material 1 [9]. As for both durability (at $-80°C$) and commutability of CAL, it is interesting to note that, for all properties with reference method values established by DGKC in 1997 and transferred values from IMEP 17 Material 1 in 2002, the values found were almost identical within uncertainty [10]. Some target values for HIGH and LOW are not physiological, e.g. 180 mmol/L for sodium and 2.40 mmol/L for potassium. Some values for the ratio HIGH/LOW deviate considerably from the expected value of 2.00. Those are 2.48 for bilirubin, 2.16 for ALT, and 2.14 for lactate dehydrogenase (LD). Because the target values of bilirubin for both HIGH and LOW are small, 12 and 5 μmol/L respectively, minor alterations, caused for instance by light influence, may change the ratio considerably. Also for ALT, the values for HIGH and LOW are small, 26 and 12 U/L, respectively. For all other properties (except for sodium and calcium), the ratios lie between 1.92 and 2.02. The fact that the ratios in general are so close to the expected value may be taken as an indication that the methods cope with the manipulated

TABLE VI. Target values for the control/reference materials used in NORIP and their relative standard uncertainties.

Property	CAL	uCAL/CAL	Source	Xt	uXt/Xt	Source	Xm	uXm/Xm	P	uP/P	H	uH/H	L	uL/L	H/L	u(H/L)
Albumin	40.516	3.25%	T	41.5	3.25%	T	41.3	3.25%	39.177	3.26%	52.51	3.26%	27.091	3.26%	1.940	0.40%
ALP	66.8		NM	72.5	*0.48%	NM	73.0	*0.50%	61.4	*0.39%	87.5	*0.79%	44.4	*0.31%	1.971	0.95%
ALT	17.8		D	24.2	*0.41%	NC	24.9	*0.73%	12.4	*1.08%	25.9	*0.65%	12.0	*0.80%	2.162	*0.76%
AMY	55.4		NM	60.7	*1.15%	NM	57.3	*0.44%	60.7	*0.32%	69.8	*0.30%	34.5	*0.34%	2.022	0.40%
AMY-P	27		NM	28.6	*0.70%	NM	29.1	*0.36%	30.2	*0.29%	37.4	*0.35%	18.6	*0.42%	2.009	0.48%
AST	23.6		NM	25.5	*0.39%	NM	25.3	*0.36%	18.0	*0.54%	29.6	*0.45%	15.5	*0.78%	1.922	0.97%
Bilirubin	8.5		D	8.97	*0.22%	NC	8.97	*0.59%	7.1	*0.76%	11.8	*0.85%	4.8	*1.27%	2.476	*1.48%
Calcium	2.2662	0.30%	T	2.325	0.34%	T	2.318	0.34%	2.297	0.35%	2.984	0.40%	2.008	0.36%	1.486	0.31%
Carbamide	4.797	0.52%	T	4.91	0.52%	T	4.90	0.56%	4.41	0.56%	6.23	0.55%	3.13	0.59%	1.994	0.32%
Cholesterol	4.901	0.23%	T	5.22	0.22%	T	5.22	0.27%	5.01	0.27%	6.69	0.28%	3.35	0.29%	1.998	0.16%
CK	118.8		D	133.3	*0.15%	NC	133.5	*0.25%	79.1	*0.27%	184.6	*0.25%	90.6	*0.44%	2.040	*0.43%
Creatininium	70.57	0.41%	T	73.9	0.41%	T	74.2	0.55%	69.6	0.56%	95.1	0.60%	49.3	0.57%	1.932	0.61%
Glucose	4.4642	0.39%	T	4.405	0.39%	T	4.405	0.43%	3.97	0.44%	5.29	0.44%	2.65	0.47%	1.998	0.28%
GT	35.835	1.35%	T	35.42	1.34%	T	35.4	1.38%	23.6	1.51%	37.5	1.38%	19.4	1.85%	1.946	1.17%
HDL-chol.	1.331		NM	1.387	*0.11%	NM	1.387	*0.19%	1.617	*0.23%	1.697	*0.23%	0.872	*0.38%	1.949	0.44%
Iron	21.163	1.40%	T	20	1.40%	T	20.0	1.42%	19.7	1.41%	26.8	1.42%	13.5	1.43%	1.990	0.31%
LD	141		NM	147.8	*1.05%	NM	148	*1.51%	130	*2.29%	199	*1.60%	94	*5.09%	2.142	4.27%
Magnesium	0.7973	0.40%	T	0.810	0.40%	T	0.810	0.51%	0.801	0.49%	1.052	0.53%	0.536	0.66%	1.967	0.64%
Phosphate	1.03		D	1.04	*0.10%	NC	1.05	*0.19%	1.08	*0.23%	1.30	*0.31%	0.66	*0.34%	1.973	*0.42%
Potassium	3.7378	0.29%	T	3.732	0.29%	T	3.74	0.31%	3.87	0.31%	4.75	0.35%	2.40	0.44%	1.982	0.43%
Protein	67.1		D	68.7	*0.08%	NC	68.7	*0.16%	68.8	*0.18%	87.1	*0.25%	44.5	*0.31%	1.961	*0.35%
Sodium	137.36	0.27%	T	140.65	0.27%	T	140.7	0.28%	141.3	0.29%	180.2	0.32%	130.8	0.30%	1.378	0.21%
TIBC	68		NM	68	*0.46%	NM	68.8	*0.28%	76.1	*0.41%	86.1	*0.37%	43.1	*0.73%	2.001	0.79%
Triglyceride	1.31	1.47%	T	1.287	1.48%	T	1.29	1.49%	1.41	1.49%	1.60	1.49%	0.81	1.50%	1.979	0.37%
Urate	290.2	0.93%	T	309.9	0.94%	T	309	0.94%	248	0.96%	407	0.96%	204	0.97%	1.997	0.33%

NORIP = Nordic Reference Interval Project; ALP = alkaline phosphatase; ALT = aspartate transaminase; AMY = amylase; AMY – P = amylase-pancreatic type; AST = aspartate transaminase; CK = creatine kinase; GT = γ-glutamyltransferase; LD = lactate dehydrogenase; TIBC = total iron-binding capacity; IFCC = International Federation of Clinical Chemistry.

The target values shown in columns titled CAL and Xt are officially certified/indicative target values, while those in columns Xm, P, H, and L are transferred values from CAL in NORIP using wet chemistry methods.

Source codes: T: Nordic Trueness Project 2002, IMEP 17, Material 1 transferred; D: DGKC 1997 reference method, NC: NORIP, CAL-transferred; NM: NORIP, mean value. Target value for TIBC in μmol/L is calculated as the mean of transferrin values measured with immunological methods in g/L using IFCC calibration and multiplied by 25.1 Where uncertainty for CAL is not given, all uncertainties given for the other controls are marked with an asterisk and represent only the uncertainty of transference.

sera HIGH and LOW in an acceptable way. The method differences are presented in Table VII.

Analytical quality specifications

The analytical quality specifications for bias (bias goals) were adapted from Fraser *et al*. [13]. The optimum goal included in these specifications, $|B| < 0.125 \cdot s_{population}$, was chosen as a criterion to select reference values to the calculations of reference intervals. As a criterion for using the common reference intervals, the minimum quality goal of $|B| < 0.375 \cdot s_{population}$ will be applied to each individual laboratory.

Mean bias for each instrument manufacturer

In principle, laboratory method bias should not affect the reference intervals, because all (non-enzyme) analytical data were corrected with CAL. Mean bias with respect to CAL for each instrument manufacturer (Table VII) is presented to give an idea of the importance of such corrections when varying methods are used. These data may also help the laboratories to assess the degree of agreement expected for their own instruments when introducing the new reference intervals. Table VII shows for each property the target value of CAL and the mean bias, the standard deviation and the number of laboratories as grouped by instrument manufacturers. For each instrument manufacturer there may be different methods represented, and some laboratories may have performed corrections of their own to original results (this is relevant only for non-enzymes).

Comments. For *albumin*, all instrument groups with more than one laboratory represented show bias values that are 3–9% higher than the target value. Considered as grouped by method (data not shown in Table VII), the bromcresol green and purple methods give both levels that are too high by 1.5 g/L, immunochemical methods by 1.0 g/L, and Ortho by 0.5 g/L. In the case of *calcium* the bias is generally positive, with the highest value of +0.12 mmol/L observed for Konelab. The bias of *cholesterol* lies between +0.2 and +0.4 mmol/L for all manufacturers. Also for *creatininium*, all bias values are positive, but this is because the target value of CAL for this property is consistent with levels obtained by using the enzyme method, while all manufacturers, with the exception of Ortho (Vitros), use the Jaffé method, and even this manufacturer has corrected its enzyme method so as to make it give results comparable with those obtained by the Jaffé method. The target value of creatininium for CAL is 70.57 μmol/L, and the mean value for the Jaffé methods is 82.5 μmol/L, for enzymatic methods 71.8 μmol/L, and for Ortho 79.5 μmol/L. The mean bias of *glucose* varies from 0.0 to +0.5 mmol/L. For *iron*, all bias values are negative but higher than −1.4 μmol/L. For *potassium*, the absolute values of the bias are extremely small, all less than 0.2 mmol/L. For *protein*, all bias values are positive and vary from 0.2 g/L (Coulter, Beckman) to 2.9 g/L (Konelab). For *sodium*, all bias values are positive, extending up to +1.9 mmol/L (Ortho), with the exception of Roche, Cobas (−1.2 mmol/L).

Harmonization of non-enzymes

The effect of correction on non-enzymes can be assessed by considering the mean deviations of the control materials X, P, HIGH and LOW after correction with CAL. The results together with those obtained for the ratio HIGH/LOW for each instrument manufacturer are presented in Table VIII.

Comments. The generally small deviations between instrument manufacturers suggest the important conclusion that all control materials are commutable, with the exception of LOW in the case of Ortho. It is well known that dry chemistry instruments have problems with diluted samples. This is reflected in the results for LOW reported in Table VIII for Ortho, notably those obtained for TIBC (−13.3%), carbamide (−7.8%), bilirubin (−6.1%), cholesterol (−4.5%) and creatininium (−4.5%).

Comparisons between materials

As has been stated above, the measurements in this project were first done on thawed serum (collected from all the reference individuals) and thawed plasma (collected from 10% of them).

TABLE VII. Mean bias for instrument manufacturers as measured by CAL.

Property	CAL target	Unit	Bias goal	Bayer, Technicon B	s	n	Coulter, Beckman B	s	n	Roche, Cobas B	s	n	Dade, Behring B	s	n	Dade, Behring (du Pont) B	s	n	Roche, Hitachi B	s	n	Konelab B	s	n	Olympus B	s	n	Ortho, Vitros B	s	n
Albumin	40.52	g/L	0.9	3.0	2.8	9	1.6	1.5	10	1.2	2.2	27	−1.7		1	−4.2		1	1.2	1.1	33	2.2	1.4	11	−3.4		1	0.5	1.7	20
ALP	66.8	U/L	7																−3	1	4							1	3	20
ALT	17.8	U/L	2	2	3	3	0	2	6	1	2	25							1	1	29	−2	2	5	1	0	2	6	3	23
AMY	55.4	U/L	8							3	3	15							5	8	10				−8		1			
AMY-P	27	U/L	5							1	2	5							−1	1	16									
AST	23.6	U/L	2	−2	4	3	0	2	6	1	2	21				1	4	2	1	2	28	−1	1	5	0		1	−1	1	19
Bilirubin	8.5	μmol/L	1.3	0.0	0.8	9	1.0	2.6	10	0.9	0.7	25				−1.8	0.7	2	0.0	0.9	33	0.6	1.2	8	1.4	0.2	2	1.1	1.5	23
Calcium	2.266	mmol/L	0.031	0.04	0.07	9	0.05	0.05	10	−0.01	0.05	25				0.07	0.04	2	0.04	0.05	33	0.12	0.07	8	0.06		1	0.05	0.08	22
Carbamide	4.797	mmol/L	0.38	0.0	0.5	6	0.2	0.3	10	0.2	0.2	23				0.2	0.3	2	0.2	0.2	33	−0.1	0.2	5	0.2	0.1	2	0.0	0.2	21
Cholesterol	4.901	mmol/L	0.15	0.4	0.1	8	0.2	0.1	10	0.2	0.2	28				0.2	0.1	2	0.2	0.2	35	0.3	0.2	8	0.3	0.0	2	0.3	0.1	20
CK	118.8	U/L	20	2	7	2	−2	8	3	−14	5	27							−10	5	25	−10	10	9	−7	6	2	−3	4	20
Creatininium	70.57	μmol/L	3	15	9	9	9	6	10	6	5	26				12	1	2	14	7	33	4	8	8	12	3	2	9	3	22
Glucose	4.464	mmol/L	0.17	0.1	0.3	4	0.2	0.1	6	0.2	0.2	24				0.4	0.0	2	0.2	0.1	28	0.2	0.1	8	0.1	0.2	3	0.2	0.1	18
GT	35.8	U/L	5													10	3	2	−1	2	28	3	3	5	−2		1	−1	2	19
HDL-chol.	1.331	mmol/L	0.12	0.03	0.20	9	0.01	0.09	10	0.02	0.06	32				0.08	0.0	2	−0.01	0.08	38	−0.03	0.07	11	−0.11	0.01	2	−0.09	0.06	4
Iron	21.16	μmol/L	2.6	−1.4	2.2	4	−0.4	1.1	8	−1.1	0.9	25				−1.8		1	−0.7	0.6	36	−1.3	1.2	4	−0.8	0.7	2	−1.1	0.7	15
LD	141	U/L	9																0	6	4									
Magnesium	0.797	mmol/L	0.02	−0.01	0.04	2	0.05	0.05	8	0.02	0.03	23				−0.05	0.06	2	0.02	0.03	22	−0.01	0.05	3	0.00		1	0.02	0.03	20
Phosphate	1.03	mmol/L	0.06	0.00	0.08	7	0.01	0.05	10	−0.03	0.04	26				0.01	0.07	2	−0.03	0.05	33	0.00	0.06	4	−0.01	0.05	2	−0.01	0.03	21
Potassium	3.738	mmol/L	0.09	0.0	0.1	7	0.0	0.1	10	0.0	0.0	27				0.1	0.0	2	0.0	0.1	32	0.1	0.0	10	0.1	0.0	2	0.0	0.1	22
Protein	67.1	g/L	1.4	1.4	2.6	6	0.2	2.8	9	0.4	1.2	18				2.4		1	1.5	2.5	24	2.9	3.3	11				1.9	1.6	14
Sodium	137.4	mmol/L	0.7	0.7	1.0	7	0.7	2.3	10	−1.2	1.5	27				1.9	0.9	2	1.2	1.6	32	0.1	1.9	10	1.8	1.2	2	1.9	1.9	22
TIBC	68	μmol/L	3.3	−7		1	−3	3	4	−1	6	4	−6	3	2				0	4	17							−3		1
Triglyceride	1.31	mmol/L	0.21	0.07	0.08	7	−0.01	0.10	10	0.01	0.04	26				−0.01	0.01	2	0.05	0.06	33	0.02	0.04	8	0.16	0.03	2	0.08	0.07	19
Urate	290.2	μmol/L	21	3	3	6	0	11	10	−12	60	24				−22	3	2	−2	11	33	0	16	9	−3	2	2	−2	11	23

ALP = alkaline phosphatase; ALT = aspartate transaminase; AMY = amylase; AMY – P = amylase-pancreatic type; AST = aspartate transaminase; CK = creatine kinase; GT = γ-glutamyltransferase; LD = lactate dehydrogenase; TIBC = total iron-binding capacity.

The column titled "CAL target" shows the target values for CAL and "Bias goal" the maximum acceptable bias values, calculated as 0.375·total biological variation. For each instrument manufacturer, "B" gives the mean deviation from the target value of CAL, "s" the standard deviation, and "n" the number of laboratories. The bias values obtained from each laboratory are usually based on means of 10 parallel measurements on CAL.

TABLE VIII. Deviations of controls from target values.

Property	Control	Bayer, Technicon	Coulter, Beckman	Dade Behring	Dade Behring (du Pont)	Konelab	Olympus	Ortho	Roche, Cobas	Roche, Hitachi
Albumin	N	8	9	1	1	10	1		26	33
	X	−0.6%	0.3%	−2.3%	−0.4%	−1.1%	−1.0%		−0.5%	−0.5%
	P	0.1%	−0.4%	−2.5%	−1.0%	−1.0%	−1.1%		0.4%	0.2%
	High	1.3%	1.8%	−1.0%	2.0%	0.7%	−3.3%		−0.4%	−0.7%
	Low	−1.1%	0.8%	0.3%	−0.5%	2.9%	6.7%		−1.3%	0.0%
	High/Low	2.6%	1.0%	−1.4%	2.3%	−2.2%	−9.4%		0.9%	−0.7%
Bilirubin	N	7	8		1	7	2	20	24	32
	X	1.1%	−1.3%		7.6%	3.0%	−1.1%	−1.2%	−2.2%	0.8%
	P	−0.5%	3.1%		2.6%	3.0%	0.6%	6.1%	0.8%	−1.8%
	High	−0.3%	−1.6%		2.4%	−0.8%	−8.1%	−8.3%	4.9%	−2.7%
	Low	−3.1%	4.9%		−1.9%	1.8%	2.8%	−6.1%	4.3%	−3.2%
	High/Low	2.8%	−4.5%		3.1%	−3.2%	−11.5%	−2.1%	−0.1%	0.2%
Calcium	N	6	9		2	7	1	21	24	33
	X	−0.4%	−0.5%		−0.4%	−2.0%	0.0%	−1.2%	0.4%	−0.3%
	P	−0.1%	−0.3%		−0.1%	−1.2%	−1.1%	−0.8%	0.6%	−0.3%
	High	0.3%	−3.0%		0.3%	−3.6%	2.5%	−1.6%	1.8%	0.0%
	Low	0.3%	1.1%		−0.6%	1.4%	−2.3%	−0.1%	−0.1%	−0.6%
	High/Low	0.0%	−4.1%		0.8%	−5.0%	4.9%	−1.6%	1.9%	0.6%
Carbamide	N	6	9		2	3	2	8	23	33
	X	−0.4%	0.2%		−0.7%	1.4%	0.4%	−1.7%	−0.6%	0.1%
	P	1.0%	−0.3%		0.8%	1.9%	−1.1%	−1.5%	−0.4%	0.0%
	High	0.5%	−0.7%		1.4%	−0.8%	0.7%	−0.5%	−0.4%	0.4%
	Low	−0.4%	2.2%		0.4%	−0.8%	1.4%	−7.8%	0.3%	−0.8%
	High/Low	0.9%	−3.0%		1.0%	−0.1%	−0.8%	7.9%	−0.8%	1.2%
Cholesterol	N	6	10		2	7	2	14	27	34
	X	−0.6%	1.0%		−0.9%	1.2%	0.2%	−0.6%	−0.2%	−0.4%
	P	−0.4%	1.1%		2.0%	0.7%	−0.6%	−1.0%	0.4%	−0.8%
	High	0.6%	−0.1%		−1.7%	2.1%	0.2%	−1.4%	0.1%	−0.6%
	Low	0.8%	−0.5%		−2.2%	1.4%	−0.3%	−4.5%	0.3%	−0.4%
	High/Low	−0.1%	0.5%		0.6%	0.8%	0.5%	3.3%	−0.2%	−0.2%
Creatininium	N	7	9		2	8	2	20	24	33
	X	1.3%	1.8%		0.5%	2.6%	1.1%	−0.1%	−0.8%	−0.4%
	P	3.3%	−0.4%		−0.6%	1.6%	1.4%	−0.6%	−1.6%	0.0%
	High	4.2%	1.0%		4.2%	−1.6%	−3.7%	8.2%	−3.4%	1.4%
	Low	0.1%	−1.0%		−8.5%	0.8%	2.5%	−4.5%	1.7%	−1.2%
	High/Low	3.9%	2.1%		13.7%	−2.4%	−6.2%	13.1%	−5.1%	2.5%
Glucose	N	2	6		2	6	1	16	23	28
	X	−1.2%	0.4%		0.8%	0.0%	0.0%	−0.1%	−0.2%	−0.1%
	P	2.0%	−0.3%		1.2%	−0.9%	−1.0%	0.1%	−0.4%	0.0%
	High	2.1%	0.3%		1.3%	0.2%	−0.7%	2.2%	0.2%	−0.3%
	Low	2.6%	−1.6%		3.9%	0.3%	−2.5%	−3.9%	−0.1%	−0.1%
	High/Low	−0.5%	1.9%		−2.5%	−0.1%	1.8%	6.4%	0.3%	−0.3%
HDL−chol.	N	7	10		2	9	2		30	38
	X	−0.8%	1.0%		−0.7%	−0.2%	−0.2%		0.3%	−0.4%
	P	−0.2%	0.2%		0.3%	−0.4%	0.3%		1.5%	−0.9%
	High	−0.9%	1.2%		0.4%	2.1%	0.1%		0.6%	−1.2%
	Low	−0.7%	−2.6%		−2.1%	2.7%	3.8%		−0.5%	0.3%
	High/Low	0.0%	4.1%		2.5%	−0.5%	−3.6%		1.0%	−1.6%
Iron	N	2	8		1	2	2		24	36
	X	−0.8%	0.3%		0.1%	2.0%	0.2%		−0.3%	−0.3%
	P	−2.8%	1.4%		−1.1%	3.0%	−1.1%		0.0%	−0.2%
	High	0.5%	−0.9%		−1.3%	5.4%	−2.7%		0.9%	−0.6%
	Low	2.4%	0.9%		−1.8%	7.3%	−1.4%		0.5%	−0.8%
	High/Low	−1.7%	−1.7%		0.4%	−1.8%	−1.4%		0.4%	0.2%

TABLE VIII. (Continued).

Property	Control	Bayer, Technicon	Coulter, Beckman	Dade Behring	Dade, Behring (du Pont)	Konelab	Olympus	Ortho	Roche, Cobas	Roche, Hitachi
Magnesium	N	2	8		2		1	18	23	22
	X	−0.5%	0.9%		2.6%		−1.2%	0.0%	−0.2%	0.1%
	P	−0.6%	1.0%		1.0%		0.2%	−0.4%	0.2%	−0.4%
	High	2.2%	2.5%		3.3%		−0.5%	2.3%	−1.8%	0.5%
	Low	−5.0%	−1.9%		−6.6%		−1.6%	−2.2%	1.5%	0.3%
	High/Low	7.4%	4.4%		10.3%		0.9%	4.5%	−3.3%	0.1%
Phosphate	N	7	10		2	2	2	20	25	33
	X	0.9%	1.2%		0.1%	0.3%	−0.3%	−0.7%	0.8%	0.5%
	P	1.4%	−2.2%		−0.5%	0.6%	0.2%	−0.3%	0.8%	−0.2%
	High	0.6%	0.3%		−0.9%	4.2%	0.1%	0.9%	−1.8%	0.9%
	Low	2.3%	2.4%		−0.1%	2.0%	0.5%	−2.2%	0.3%	−1.6%
	High/Low	−1.7%	−1.8%		−0.8%	2.1%	−0.5%	3.1%	−2.1%	2.4%
Potassium	N	6	8		2	6	2	21	26	31
	X	−0.5%	0.4%		0.2%	0.1%	−0.2%	−0.5%	0.3%	0.2%
	P	0.0%	0.5%		0.4%	−1.1%	−0.5%	−0.2%	0.2%	0.1%
	High	1.0%	1.0%		0.4%	−4.2%	0.0%	−0.9%	0.3%	0.4%
	Low	0.4%	−1.8%		−0.6%	5.2%	4.4%	−0.9%	−0.9%	−0.4%
	High/Low	0.6%	2.8%		0.9%	−8.9%	−4.3%	0.0%	1.1%	0.7%
Protein	N	5	9		1	8		14	18	24
	X	−0.4%	0.3%		−1.2%	0.2%		−0.3%	0.2%	0.0%
	P	0.2%	0.4%		−0.5%	0.1%		−0.1%	0.3%	−0.4%
	High	2.4%	−0.7%		1.1%	1.5%		1.8%	−0.6%	−0.3%
	Low	3.0%	0.0%		−0.2%	2.0%		0.3%	−1.1%	−0.4%
	High/Low	−0.5%	−0.7%		1.3%	−0.5%		1.5%	0.6%	0.1%
Sodium	N	6	9		2	9	2	20	26	30
	X	−0.2%	−0.1%		−0.1%	0.0%	−0.6%	−0.4%	0.2%	0.2%
	P	0.1%	−0.2%		0.5%	−0.4%	−0.6%	−0.1%	0.3%	0.0%
	High	0.5%	−0.8%		−0.3%	−1.8%	−0.4%	−0.5%	0.7%	0.2%
	Low	−0.7%	−0.8%		1.1%	2.1%	0.2%	−1.3%	−0.1%	−0.1%
	High/Low	1.2%	0.0%		−1.4%	−3.9%	−0.6%	0.8%	0.9%	0.3%
TIBC	N		3	2				1	4	17
	X		2.0%	0.5%				1.5%	0.9%	1.2%
	P		−0.5%	−1.2%				−5.2%	1.0%	0.0%
	High		−1.6%	0.2%				−1.5%	−0.1%	0.3%
	Low		−0.9%	0.3%				−13.3%	2.9%	−0.6%
	High/Low		−0.9%	−0.1%				13.4%	−2.6%	0.8%
Triglyceride	N	6	9		2	5	2	17	25	31
	X	0.0%	0.6%		1.1%	0.2%	−0.7%	0.7%	0.1%	−0.6%
	P	1.0%	−0.2%		1.1%	−2.5%	0.6%	1.5%	0.2%	0.2%
	High	−1.0%	2.4%		−0.5%	0.3%	−1.2%	1.7%	−0.3%	−0.3%
	Low	2.8%	0.3%		−1.2%	−1.2%	1.1%	−2.9%	0.1%	−0.4%
	High/Low	−3.7%	2.1%		0.6%	1.5%	−2.3%	4.6%	−0.4%	0.1%
Urate	N	6	10		2	6	2	22	22	33
	X	−0.5%	−0.8%		1.3%	−0.5%	−1.5%	−0.9%	−1.0%	0.3%
	P	1.4%	1.9%		−2.8%	1.0%	−3.0%	−0.6%	−1.7%	0.5%
	High	2.7%	−3.1%		0.3%	1.4%	−2.2%	1.7%	−0.3%	0.5%
	Low	0.8%	3.2%		3.8%	1.5%	−0.9%	−3.2%	−0.1%	−1.5%
	High/Low	1.9%	−6.1%		−3.4%	−0.1%	−1.3%	5.0%	−0.3%	2.0%

Deviations are expressed in percent of the respective target values (Table VI) for all controls and instrument manufacturers after correction with CAL. The quotient HIGH/LOW with the target value of 2.00 (not valid for sodium and calcium) is also considered (target value used is specific for each property and is the median for all laboratories).

N is the number of laboratories.

However, the laboratories were encouraged also to measure on fresh materials. Therefore, the data obtained from some laboratories cover both fresh and thawed samples of both serum and plasma. This made it possible to compare various combinations of these materials against

quality goals and to assess the need to establish separate reference intervals for different materials. Comparisons such as those focused on individual instrument manufacturers may also provide the participating laboratories with useful data for evaluation of their methods before introducing the new reference intervals (such data are not shown in this report, however). Data for the comparisons fresh plasma vs. thawed serum, thawed serum vs. fresh serum, thawed plasma vs. fresh plasma, and fresh plasma vs. fresh serum are presented in Table IX. To evaluate the concentration dependence of any difference, Passing-Bablock regression plots are available on the project home site [2]. These plots also show whether there are significant deviations in the slope and the intercept from the ideal values (1 and 0, respectively).

Comments. As compared to bias goals (calculated as 0.375·biological variation), the difference between thawed and fresh serum was unimportant for each of the properties. Between fresh plasma and fresh serum, there were important differences for glucose (0.22 mmol/L), potassium (−0.16 mmol/L), and protein (1.6 g/L). Similar differences were also observed for these properties between fresh plasma and thawed serum. Between thawed and fresh plasma, only TIBC showed an important difference (4 μmol/L). Supplementary data available on the home site of this project [2] show some important differences between plasma and serum for specific instrument manufacturers: Roche, Cobas has generally much higher plasma values than serum values for bilirubin, with great dispersion in differences. Konelab seems to detect substantially lower carbamide levels in plasma than the other manufacturers. For potassium, the plasma levels are lower than serum levels, and the absolute difference between these materials increases with increasing potassium concentrations, the Passing-Bablock regression line being as follows: fresh plasma = 0.933 × thawed serum + 0.11 (mmol/L). Enzymes are not considered in this report.

Precision

Precision was expressed as a coefficient of variation (CV) for each property and instrument manufacturer. The CV for each laboratory CV was calculated as: $CV_{Lab} = \sqrt{[(CV_{CAL}{}^2 + CV_X{}^2 + CV_P{}^2 + CV_{HIGH}{}^2 + CV_{LOW}{}^2)/5]}$. These values were averaged over the laboratories to obtain a mean CV for each instrument manufacturer: $\sqrt{(\Sigma CV_{Lab}{}^2/N)}$, where N is the number of laboratories. The results are presented in Table X.

Comments. Konelab had the worst precision on 9 of the 25 properties, Coulter Beckman on 7, Bayer and Ortho each on 4, and both instrument groups represented by Roche (Cobas and Hitachi) on 0. Median %CV for all properties was best for Olympus, but only 2 laboratories used this instrument. Of the major instrument manufacturers, Ortho and Roche (Cobas and Hitachi) were the best ones, while Konelab was the worst also as assessed by using this criterion. Laboratories were not excluded on the basis of precision evaluation alone.

Exclusion of data

The principles of exclusion are presented elsewhere [1]. For each property, the criteria and number of excluded results for thawed serum are listed in Table XI.

Comments. Testing for differences between materials (cf. also discussion above) is particularly important for properties with low biological variation. The following properties had the highest number of reference values excluded because of such differences: potassium (94 excluded reference values, which amount to 3.4% of the reference values obtained for this property), calcium (81 reference values, or 3.0%), and sodium (59 reference values, or 2.1%). A closer look at the excluded values after the reference intervals had been calculated showed that only 2 of the excluded 94 potassium values were outside the final reference limits, 13 of the 81 for calcium, and all excluded values for sodium. Hence, exclusion of reference values affected only the reference intervals of sodium, tending to narrow these.

TABLE IX. Differences between materials.

Property	Unit	Goal	Fresh plasma – thawed serum			Thawed serum – fresh serum			Thawed plasma – fresh plasma			Fresh plasma – fresh serum		
			d	s	n	d	s	n	d	s	n	d	s	n
Albumin	g/L	0.9	−0.3	1.4	1114	−0.1	1.4	696	−0.3	1.4	81	−0.4	1.2	816
ALP	U/L	7	−1	2	91	−1	2	62				−1	2	79
ALT	U/L	2	0	5	811	−2	4	608	−1	2	41	−2	2	601
AMY	U/L	8	−2	3	307	0	2	252	3	4	57	−2	2	255
AMY-P	U/L	5	−1	1	193	1	1	65	−1	1	8	0	1	89
AST	U/L	2	0	2	871	0	2	586	2	2	33	0	2	712
Bilirubin	µmol/L	1.3	0.0	2.0	795	−0.1	1.3	722	−0.7	1.2	21	−0.1	0.9	543
Calcium	mmol/L	0.032	−0.023	0.054	995	0.004	0.053	648	−0.002	0.059	49	−0.027	0.043	772
Carbamide	mmol/L	0.38	−0.09	0.22	892	0.04	0.25	668	−0.03	0.17	50	−0.07	0.18	662
Cholesterol	mmol/L	0.15	−0.12	0.24	1158	0.03	0.21	705	0.00	0.27	81	−0.10	0.18	840
CK	U/L	20	2	12	714	−4	12	482	−1	3	50	−2	6	612
Creatininium	µmol/L	3.3	−0.4	3.8	1088	0.1	3.9	720	0.3	2.6	81	−0.3	2.8	828
Glucose	mmol/L	0.17	0.25*	0.22	460	−0.04	0.20	315	−0.03	0.12	43	0.22*	0.19	357
GT	U/L	5	−1	4	522	0	2	295	1	2	21	0	2	374
HDL-chol.	mmol/L	0.12	−0.01	0.13	1083	−0.01	0.08	672	−0.03	0.08	72	−0.02	0.06	815
Iron	µmol/L	2.6	−0.5	1.1	925	0.0	1.0	649	0.4	0.7	67	−0.5	0.7	771
Magnesium	mmol/L	0.021	−0.003	0.031	813	−0.003	0.028	461	0.010	0.025	48	−0.010	0.024	547
Phosphate	mmol/L	0.06	−0.05	0.05	1044	0.00	0.05	666	0.00	0.05	81	−0.05	0.04	776
Potassium	mmol/L	0.09	−0.15*	0.13	956	−0.01	0.10	684	0.04	0.09	62	−0.16*	0.12	720
Protein	g/L	1.4	1.7*	2.0	706	−0.3	2.0	564	0.4	2.0	12	1.6*	1.8	684
Sodium	mmol/L	0.7		1.8	1072	0.0	1.7	691	0.2	1.5	75	−0.6	1.2	821
TIBC	µmol/L	3	−3	5	91	2	3	46	4*	19	6	−2	2	68
Triglyceride	mmol/L	0.21	−0.03	0.08	624	0.02	0.08	391	0.02	0.08	48	−0.03	0.06	468
Urate	µmol/L	20.9	−0.5	10.8	896	2.2	13.9	654	−0.4	9.9	72	0.0	7.9	620

ALP = alkaline phosphatase; ALT = aspartate transaminase; AMY = amylase; AMY – P = amylase-pancreatic type; AST = aspartate transaminase; CK = creatine kinase; GT = γ-glutamyltransferase; LD = lactate dehydrogenase; TIBC = total iron-binding capacity.

Mean (d), standard deviation (s) and number (n) of differences are shown for each comparison. A mean of differences is marked with an asterisk (*) if its absolute value is greater than the respective bias goal (calculated as 0.375·total biological variation).

TABLE X. Mean within-series coefficients of variation based on all control values.

Property	Bayer, Technicon	Coulter, Beckman	Dade Behring (du pont)	Konelab	Olympus	Ortho, Vitros	Roche, Cobas	Roche, Hitachi
Albumin	2.8%	2.5%	1.2%	2.7%	1.2%	3.1%	1.7%	1.6%
ALP	2.9%	2.6%	4.3%	3.3%	1.3%	1.8%	2.2%	1.7%
ALT	6.0%	11.6%	9.3%	6.9%	5.3%	7.7%	4.4%	6.2%
AMY	3.3%	3.4%	1.7%	4.4%	1.0%	5.6%	2.9%	1.9%
AMY-P	6.1%	2.8%				2.2%	1.4%	2.5%
AST	5.5%	6.9%	6.1%	6.6%	2.6%	2.9%	3.7%	5.6%
Bilirubin	11.5%	17.6%	14.1%	5.2%	4.1%	6.8%	5.8%	7.6%
Calcium	1.8%	2.2%	1.2%	3.4%	1.3%	2.2%	1.5%	1.4%
Carbamide	2.5%	4.4%	2.4%	3.3%	2.7%	2.6%	2.7%	2.8%
Cholesterol	3.0%	2.3%	1.9%	3.9%	1.4%	2.0%	1.4%	1.7%
CK	4.6%	3.3%	1.6%	4.4%	0.7%	3.9%	2.1%	1.4%
Creatininium	4.5%	3.2%	2.8%	6.3%	0.8%	1.4%	2.4%	2.6%
Glucose	3.6%	2.4%	1.6%	3.5%	1.6%	2.1%	1.7%	1.9%
GT	5.4%	8.2%	2.6%	4.5%	1.7%	2.1%	2.6%	2.1%
HDL-chol.	2.9%	3.3%	3.2%	4.7%	4.2%	3.8%	2.5%	2.3%
Iron	2.3%	2.7%	1.4%	2.9%	1.7%	3.4%	1.6%	3.0%
LD	3.9%	2.8%	2.1%	4.1%	1.1%	3.1%	2.8%	1.6%
Magnesium	1.7%	3.1%	1.8%	6.5%	1.2%	2.8%	3.1%	4.0%
Phosphate	3.2%	4.0%	2.4%	4.9%	1.6%	2.3%	1.8%	2.4%
Potassium	1.5%	2.2%	1.6%	1.4%	1.4%	1.5%	0.9%	1.3%
Protein	4.1%	2.5%	1.0%	3.6%		1.9%	1.3%	1.3%
Sodium	0.7%	2.0%	0.9%	0.7%	1.1%	1.0%	0.6%	0.9%
TIBC		2.1%				4.0%	3.2%	2.4%
Triglyceride	3.9%	4.2%	2.3%	4.4%	2.2%	1.8%	1.8%	2.8%
Urate	2.9%	2.2%	2.9%	3.4%	1.4%	1.6%	2.0%	1.2%
Mean no. of labs	5.2	7.1	1.9	6.7	1.8	17	21	29
Median %CV	3.3%	2.8%	2.1%	4.1%	1.4%	2.3%	2.1%	2.1%
No. with worst precision	4	7	1	9	0	4	0	0

ALP = alkaline phosphatase; ALT = aspartate transaminase; AMY = amylase; AMY – P = amylase-pancreatic type; AST = aspartate transaminase; CK = creatine kinase; GT = γ-glutamyltransferase; LD = lactate dehydrogenase; TIBC = total iron-binding capacity.

"Mean no. of labs" refers to the mean number of laboratories as averaged over the properties. "Median %CV" is the median coefficient of variation as calculated over the properties.

"No. with worst precision" is the number of properties for which the respective manufacturer showed the worst precision.

REFERENCE INTERVALS

Method

Reference limits were determined as the 2.5 and 97.5 percentiles of reference distributions by applying the simple non-parametric method. The RefVal 4.0 program [6], which implements the IFCC recommendations for calculations of reference intervals, was used for these calculations.

Subgroups

Each participating laboratory was requested to collect reference samples from individuals as distributed evenly on age and gender. Because of this arrangement, distributions by some other parameters, such as geography and analytical method, should be similar in subgroups defined by age and gender. A project-specific version of RefVal 4.0, modified so as to implement proportion criteria for partitioning as described by Lahti *et al.* [7], was used to perform partitioning calculations in this project. Proportions of $<0.9\%$ or $>4.1\%$ of two subgroups falling outside a reference limit for their combined distribution were used as criteria to establish separate reference intervals for those subgroups. Subsequent assessment of clinical usefulness may in some cases have resulted in different conclusions from those suggested by application of these criteria, however. Only gender and age have so far been considered systematically as stratification categories, but for some properties other categories were also examined.

TABLE XI. Number of excluded data for thawed serum.

Property	Total	Rest	% deleted	Ind	Dupl	Mat	Enz	Sno	Oestr	Phys	Non-fasting	Dia	Outl	OutlR	Meth	UIBC	Fe <6	Other
Albumin	2819	2709	3.9%	23	32	29		7							19			
ALP	2477	495	80%	20	480		1982	2					1					2
ALT	2754	2301	16%	23	32		426	7					3					
AMY	2021	719	64%	16	32		1294						1					
AMY-P	850	497	42%	9			342	2										
AST	2452	2142	13%	19	32		287	7					6					
Bilirubin	2818	2740	2.8%	23	32	16		7										
Calcium	2703	2571	4.9%	23		81		7										23
Carbamide	2584	2535	1.9%	21		2		7							19			
Cholesterol	2766	2735	1.1%	23		1		7										1
CK	2641	1851	30%	22	32	1	530	29		374			11					1
Creatininium	2709	2636	2.7%	21	32	13		7										
Glucose	2358	919	61%	21		11		37			1278	275						
GT	2557	1382	46%	21	30	2	1162	32					4					1
HDL-chol.	2637	2603	1.3%	23		4		7										1
Iron	2370	2292	3.3%	20				7							32		19	
LD	2376	0	100%	20	482		2376	39							62			
Magnesium	2198	2123	3.4%	14		25		35										2
Phosphate	2656	2595	2.3%	22		1		7							32			
Potassium	2757	2608	5.4%	23		94		32										1
Protein	2097	1985	5.3%	18	32	31		5						1	25			
Sodium	2763	2642	4.4%	23	32	59		7										
TIBC	942	668	29%	6				2	156							111		25
Triglyceride	2714	1203	56%	23		1		7			1492							
Urate	2708	2622	3.2%	23	32	4		7							19			1

ALP = alkaline phosphatase; ALT = aspartate transaminase; AMY = amylase; AMY – P = amylase-pancreatic type; AST = aspartate transaminase; CK = creatine kinase; GT = γ-glutamyltransferase; LD = lactate dehydrogenase; TIBC = total iron-binding capacity.

Ind: All data for one person excluded because of two extreme values for different properties.

Dupl: Re-measurement of a sample by using another measurement system, only one of the results used in calculations.

Mat: When two values for the same individual and property were compared between different materials, the value deviating more from the median was deleted if the difference between the two values exceeded 1.5·biological variation.

Enz: Enzyme method not IFCC (37°C) compatible.

Sno: Missing control values.

Oestr: Oestrogen use by a reference person.

Phys: Heavy physical activity.

Nonfast: Non-fasting (< 12 h from last meal).

Dia: Diabetes in family.

Outl: Outlier for enzymes, defined as a value outside mean ± 4 standard deviations for log-transformed data.

OutlR: Outlier by Dixon's test as implemented in the Refval 4.0 program.

Meth: Insufficient method data.

UIBC: UIBC method used instead of TIBC method.

Fe <6: values of < 6 μmol/L excluded.

Other: Other reasons, e.g. ionized calcium measured instead of total calcium and great dispersion of reference values for one TIBC method.

Gender and age. Partitioning by gender is straightforward to perform by using the modified RefVal 4.0 program. Age dependence for each gender was assessed, first by investigating the reference limits for each of the age groups 18 – 29, 30 – 39, 40 – 49, 50 – 59, 60 – 69 and ≥ 70 years. If dependence on age seemed to exist, this dependence was tested with the modified RefVal 4.0 program by selecting an appropriate age as a limit between potential subgroups. For some properties, two such limits were determined. Reference intervals for each gender and age group are presented in Table XII.

TABLE XII. Gender- and age-specific reference intervals.

		Both genders							Female							Male						
Property		18 29	30 39	40 49	50 59	60 69	70 90	All	18 29	30 39	40 49	50 59	60 69	70 90	All	18 29	30 39	40 49	50 59	60 69	70 90	All
Albumin	N	667	343	489	567	192	450	1209	349	180	275	309	87	233	629	318	163	214	258	105	217	580
	2.5	36.2	37.3	36.6	36.3	36.3	34.4	35.1	35.5	36.8	35.9	36.4	34.7	33.7	34.7	39.0	39.5	37.4	36.2	36.6	34.8	35.6
	97.5	48.0	47.3	45.5	45.5	46.0	44.2	45.3	47.2	46.5	45.2	45.5	44.5	43.6	45.0	48.8	48.2	45.6	45.6	46.1	44.4	45.5
Bilirubin	N	678	350	494	571	193	452	1216	356	182	277	311	87	235	633	322	168	217	260	106	217	583
	2.5	4.2	4.9	4.5	4.8	5.3	5.2	5.1	3.7	4.6	3.9	4.5	4.5	4.9	4.7	5.4	5.6	5.4	5.5	6.4	5.6	5.6
	97.5	25.1	24.1	24.4	23.2	26.0	23.5	23.4	22.8	21.7	21.8	22.1	22.9	21.3	21.3	29.2	28.6	30.0	24.9	30.5	24.7	25.5
Calcium	N	629	309	469	536	185	441	1162	333	159	266	297	83	227	607	296	150	203	239	102	214	555
	2.5	2.20	2.18	2.16	2.17	2.20	2.17	2.17	2.20	2.16	2.14	2.16	2.20	2.17	2.16	2.25	2.22	2.18	2.19	2.19	2.17	2.17
	97.5	2.51	2.50	2.49	2.52	2.53	2.53	2.52	2.49	2.48	2.48	2.52	2.50	2.55	2.52	2.54	2.54	2.49	2.52	2.55	2.51	2.52
Calcium, corr.	N	619	304	462	530	183	436	1149	327	156	261	293	82	224	599	292	148	201	237	101	212	550
	2.5	2.21	2.17	2.19	2.20	2.22	2.22	2.21	2.20	2.16	2.18	2.21	2.24	2.26	2.22	2.22	2.19	2.19	2.20	2.20	2.20	2.20
	97.5	2.47	2.47	2.47	2.52	2.52	2.54	2.53	2.48	2.47	2.47	2.51	2.52	2.60	2.53	2.46	2.47	2.48	2.52	2.52	2.52	2.52
Carbamide	N	626	322	462	521	183	419	1123	328	172	261	284	84	217	585	298	150	201	237	99	202	538
	2.5	2.67	2.75	2.96	3.16	3.53	3.42	3.32	2.48	2.62	2.84	2.96	3.39	3.28	3.11	3.12	3.12	3.30	3.44	3.57	3.78	3.64
	97.5	7.02	7.07	7.38	7.62	8.54	9.02	8.23	6.19	5.68	6.79	7.37	8.27	9.00	7.97	7.96	7.65	7.79	8.04	8.79	9.03	8.50
Cholesterol	N	674	349	494	572	191	453	1216	354	182	278	311	87	236	634	320	167	216	261	104	217	582
	2.5	2.9	3.3	3.6	4.0	4.1	4.0	4.0	3.0	3.3	3.6	4.0	4.6	4.2	4.1	2.8	3.3	3.5	4.1	3.9	3.8	4.0
	97.5	6.1	6.9	6.9	7.7	7.8	8.2	7.9	6.1	6.2	6.8	7.5	8.1	8.6	8.1	6.3	7.6	7.3	7.9	7.8	7.6	7.7
Creatininium	N	641	338	471	557	181	446	1184	336	176	262	307	81	229	617	305	162	209	250	100	217	567
	2.5	53	52	56	53	52	54	53	50	50	52	50	50	53	51	64	63	64	62	64	63	63
	97.5	94	90	95	94	99	103	99	83	83	83	83	91	90	88	97	93	99	100	103	109	103
Glucose	N	236	110	140	174	72	186	432	132	49	75	97	31	98	226	104	61	65	77	41	88	206
	2.5	3.91	4.06	4.02	3.93	4.24	4.23	4.24	3.82	3.96	3.85	3.79	–	4.20	4.20	3.96	4.15	4.29	3.95	4.09	4.27	4.26
	97.5	5.41	6.17	5.84	6.10	5.82	6.29	6.18	5.40	5.57	5.87	6.06	–	5.97	5.98	5.55	6.80	6.06	6.52	5.78	6.34	6.30
HDL-chol.	N	643	322	478	543	181	434	1158	336	170	268	295	83	227	605	307	152	210	248	98	207	553
	2.5	0.85	0.82	0.90	0.89	0.94	0.93	0.92	1.03	1.04	1.10	1.00	0.97	0.95	1.00	0.81	0.72	0.78	0.84	0.92	0.87	0.86
	97.5	2.36	2.24	2.32	2.54	2.61	2.59	2.60	2.50	2.37	2.42	2.68	2.84	2.76	2.72	1.86	2.05	2.12	2.09	2.15	2.30	2.16
Iron	N	568	276	419	482	162	383	1027	297	146	235	262	75	202	539	271	130	184	220	87	181	488
	2.5	8.6	8.2	8.4	9.8	10.4	10.7	10.3	8.4	7.7	7.7	9.5	9.1	9.7	9.7	9.6	9.1	10.6	10.5	12.0	11.7	11.4
	97.5	35.0	34.3	33.4	33.3	33.8	31.5	32.1	37.3	34.0	33.3	33.8	28.3	28.3	31.5	34.6	35.1	34.9	31.5	37.3	33.7	33.5
Iron sat.	N	143	95	120	123	57	125	305	51	44	67	46	25	62	133	92	51	53	77	32	63	172
	2.5	0.13	0.13	0.11	0.15	0.16	0.16	0.16	0.12	0.10	0.10	0.12	–	0.15	0.14	0.14	0.15	0.17	0.18	–	0.16	0.18
	97.5	0.56	0.56	0.57	0.51	0.45	0.58	0.52	0.62	0.50	0.55	0.50	–	0.56	0.50	0.57	0.60	0.70	0.53	–	0.65	0.56
LDL-chol.	N	275	133	177	235	102	242	579	153	71	101	127	49	131	307	122	62	76	108	53	111	272
	2.5	1.25	1.44	1.33	1.96	1.90	2.01	1.98	1.15	1.28	1.29	1.67	1.89	2.04	1.90	1.39	1.72	1.33	2.10	1.60	2.00	2.00
	97.5	4.29	4.64	4.85	5.21	5.50	5.64	5.35	4.23	4.13	4.50	4.89	5.91	6.13	5.47	4.35	5.54	4.93	5.76	5.09	5.15	5.21

TABLE XII. (Continued).

Property		Both genders							Female							Male						
		18 29	30 39	40 49	50 59	60 69	70 90	All	18 29	30 39	40 49	50 59	60 69	70 90	All	18 29	30 39	40 49	50 59	60 69	70 90	All
Magnesium	N	527	283	383	433	157	338	928	278	153	219	240	71	180	491	249	130	164	193	86	158	437
	2.5	0.70	0.70	0.71	0.70	0.70	0.71	0.71	0.70	0.69	0.70	0.70	0.69	0.71	0.71	0.71	0.71	0.72	0.71	0.70	0.71	0.72
	97.5	0.92	0.95	0.92	0.96	0.97	0.93	0.95	0.91	0.92	0.92	0.94	0.97	0.94	0.95	0.95	0.96	0.93	0.98	0.97	0.93	0.97
Phosphate	N	641	323	469	540	183	437	1160	331	170	262	293	84	225	602	310	153	207	247	99	212	558
	2.5	0.87	0.82	0.76	0.78	0.80	0.74	0.77	0.90	0.84	0.77	0.85	0.89	0.84	0.85	0.82	0.79	0.74	0.74	0.76	0.70	0.74
	97.5	1.63	1.49	1.47	1.41	1.46	1.42	1.42	1.53	1.47	1.47	1.48	1.53	1.44	1.47	1.70	1.55	1.47	1.38	1.32	1.29	1.33
Potassium	N	646	329	486	541	177	427	1145	339	175	270	295	81	220	596	307	154	216	246	96	207	549
	2.5	3.59	3.63	3.60	3.62	3.55	3.69	3.62	3.56	3.60	3.57	3.57	3.60	3.67	3.60	3.61	3.68	3.63	3.65	3.54	3.69	3.64
	97.5	4.59	4.57	4.62	4.62	4.63	4.77	4.69	4.54	4.57	4.59	4.61	4.60	4.70	4.65	4.63	4.60	4.69	4.68	4.65	4.79	4.74
Protein	N	489	249	354	402	147	343	892	247	128	196	209	70	176	455	242	121	158	193	77	167	437
	2.5	63.6	63.9	62.0	62.6	62.9	61.0	62.0	63.6	63.2	61.5	62.4	62.3	60.6	61.5	63.4	64.0	62.8	62.8	62.0	61.7	62.3
	97.5	79.0	81.3	76.3	76.1	77.8	78.6	77.2	78.8	77.5	76.3	76.4	80.4	78.4	77.1	79.3	82.3	76.9	75.9	77.2	78.7	77.3
Sodium	N	650	335	484	547	186	438	1171	342	177	271	302	84	229	615	308	158	213	245	102	209	556
	2.5	137	136	137	137	136	137	137	136	136	136	136	136	137	137	137	136	138	137	136	137	137
	97.5	144	144	145	145	146	145	145	144	144	144	145	146	145	145	145	145	146	145	146	145	145
TIBC	N	144	95	123	124	57	125	306	52	44	69	46	25	62	133	92	51	54	78	32	63	173
	2.5	49	52	47	51	49	49	49	45	44	48	45	–	49	49	49	52	45	52	–	44	49
	97.5	82	85	87	79	94	82	81	85	87	95	79	–	82	83	81	83	83	79	–	83	81
Triglyceride	N	284	138	184	242	104	249	595	157	72	103	129	50	134	313	127	66	81	113	54	115	282
	2.5	0.42	0.48	0.45	0.51	0.45	0.54	0.52	0.41	0.41	0.41	0.48	0.24	0.56	0.52	0.43	0.50	0.46	0.51	0.53	0.48	0.52
	97.5	2.80	3.35	2.89	2.56	2.21	2.47	2.45	2.86	2.03	2.22	2.51	2.10	2.49	2.34	2.80	4.04	4.67	3.02	2.65	2.50	2.51
Urate	N	643	333	475	548	184	437	1169	337	174	269	296	86	226	608	306	159	206	252	98	211	561
	2.5	157	151	159	178	188	191	185	147	145	150	167	163	177	170	231	242	234	221	206	240	223
	97.5	443	459	441	437	482	454	455	341	343	369	383	424	400	394	468	481	472	460	499	474	480

TIBC = total iron-binding capacity.

The rows titled "2.5" and "97.5" show the non-parametric percentiles and the row titled "N" the number of reference values in each distribution (these distributions concern thawed serum). Six age intervals are considered, and the columns titled "All" show the data for combined age groups.

A minus (−) indicates that the number of reference values was insufficient to allow calculation of reference limits.

Comment. Partitioning with respect to age being necessarily somewhat arbitrary, the original data available on the web site of NORIP [2] allowed readers personally to assess the age stratifications suggested in Table XII. These original data could also be used to establish regression-based, age-dependent continuous reference intervals, should someone wish to apply that approach. Special attention should be paid to the uncertainties of reference limits, because these grow as the number of reference values in the subgroups decreases. Age dependence seems, however, evident for albumin, phosphate for men, cholesterol and carbamide (urea). Even if calcium was not partitioned on age, age dependence of albumin also makes albumin-corrected calcium age-dependent.

Geography. It is not self-evident that the same reference intervals are applicable in each of the Nordic countries [14]. To examine this issue, country-specific reference limits were compared with those of the combined distributions, as subgroups both undivided and divided by gender (a different approach from the one outlined by Lahti [14]). The results are presented in Table XIII. The prevalences of country populations were not accounted for.

Comment. The numbers of reference values obtained from Iceland were small, which might be the reason why the reference limits calculated for this country often deviate from the common limits. However, uncertainty about those reference limits is large, and the impact of the data from Iceland on the combined distributions remains negligible. There are many deviations of the country-specific limits from those of the combined distributions. The most pronounced of these are (observe that most of the data in the following list are not presented explicitly in Table XIII):

- carbamide, upper reference limit of the distribution for Danish men: -0.44 mmol/L
- glucose, upper reference limit of the distribution for Danish men: $+0.24$ mmol/L
- protein, upper reference limit of the distribution for Danish men: $+3$ g/L
- sodium, lower reference limit of the distribution for Danish women: $+1.1$ mmol/L
- sodium, lower reference limit of the distribution for Norwegian women: -1.4 mmol/L
- TIBC (measured mainly in Norway and Sweden), lower reference limit of the distribution for Swedish women: $+3.9$ μmol/L
- TIBC, upper reference limit of the distribution for Swedish men: $+4.7$ μmol/L
- urate, lower reference limit of the distribution for Icelandic women: -27 μmol/L

BMI. Plots and regression equations for concentration vs. body mass index (BMI) curves are presented on the project home site [2]. In Table XIV differences between results obtained for subjects with a BMI of <27 kg/m^2 and those with a BMI of ≥ 27 kg/m^2 for each gender and property are presented, and whether these differences are statistically significant ($p<0.05$) or not, as evaluated by Student's *t*-test.

Comment. Cholesterol (mmol/L) increases with BMI (kg/m^2) following the linear regression curve cholesterol $= 0.068 \cdot \text{BMI} + 3.6$ (mmol/L) and glucose (mmol/L) for men according to glucose $= 0.044 \cdot \text{BMI} + 3.9$ (mmol/L) and for women according to glucose $= 0.053 \cdot \text{BMI} + 3.5$ (mmol/L). HDL-chol. decreases with increasing BMI.

Reference value distribution(s)

Frequency distributions of reference values combined with cumulative standard normal deviate (z-score) plots for each property and the suggested subgroups are shown on the web site of this project [2].

NORIP proposal compared to reference intervals found in textbooks. Proposed reference intervals together with suggested stratifications and other central results of this project are presented in detail elsewhere [1]. Enzymes are discussed by Strømme *et al.* [4]. In Table XV, the new reference intervals proposed for non-enzymes by NORIP are compared with suggestions given in the textbooks of clinical chemistry edited by Tietz [15] and Laurell [16]. The textbook by Laurell was selected as one source of comparative data, because,

TABLE XIII. Deviations of country-specific reference limits from common limits (thawed serum) as expressed in property units.

			All		Denmark		Finland		Iceland		Norway		Sweden	
Property	Bias goal	Gender	Low	High	Low	High	Low	High	Low	High	Low	High	Low	High
Albumin	0.9	FM	36	47	0	1	−1 *	0	1	3 *	1	0	0	0
Bilirubin	1.3	FM	5	24	−1	0	1	5 *	−1 *	5 *	0	−4 *	0	0
Calcium	0.032	FM	2.18	2.51	0.02	0.03	−0.01	−0.01	−0.01	0.02	0.00	0.00	0.01	0.00
Calcium, corr.	0.032	FM	2.20	2.50	0.01	0.03	−0.02	0.00	−0.03	0.05 *	0.00	−0.01	0.00	0.00
Carbamide	0.38	F	2.7	7.4	0.0	0.0	0.0	0.0	−0.4 *	−1.2 *	0.1	0.2	0.0	0.2
		M	3.4	8.2	−0.2	−0.4 *	0.1	0.3	−	−	0.1	−0.1	−0.1	0.1
Cholesterol	0.15	FM	3.3	7.5	0.0	0.2 *	0.0	−0.3 *	0.2 *	0.2 *	0.1	0.3 *	−0.1	−0.2 *
Creatininium	3.3	F	51	84	−1	2	1	1	−	−	0	−4 *	−1	5 *
		M	64	100	−2	−6 *	1	−1	−	−	−1	0	2	4 *
Glucose	0.17	FM	4.0	6.0	−0.1	0.2	0.0	0.0	−	−	0.1	−0.1	−0.1	0.0
HDL-chol.	0.12	F	1.0	2.6	0.0	−0.1	0.1	0.1	0.0	−0.3 *	0.0	0.1	−0.1	−0.1
		M	0.8	2.1	0.0	0.0	0.0	0.0	−	−	−0.1	0.0	0.0	−0.1
Iron	2.6	FM	9.2	33.7	−0.3	−1.2	0.5	0.4	−1.7	−1.5	0.0	0.1	0.3	0.4
Iron sat.	0.102	F	0.12	0.50	−	−	−	−	−	−	0.00	0.04	0.00	−0.07
		M	0.16	0.57	−	−	−	−	−	−	0.00	0.00	−0.01	0.06
LDL-chol.	0.338	FM	1.5	5.1	−0.2	0.0	0.0	−0.2	−	−	0.0	0.1	0.0	0.0
Magnesium	0.021	FM	0.71	0.94	0.01	0.01	0.03 *	0.00	−0.06 *	0.04 *	−0.01	0.00	0.02	0.00
Phosphate	0.06	F	0.85	1.49	0.03	−0.02	−0.05	−0.02	−0.02	0.01	0.00	0.01	−0.02	0.00
		M	0.75	1.56	0.03	−0.05	0.02	0.01	−	−	−0.04	0.02	−0.05	−0.01
Potassium	0.09	FM	3.6	4.6	0.1	0.0	0.0	−0.1 *	0.0	−0.1	0.0	0.1 *	0.0	0.0
Protein	1.4	FM	62	78	−1	3 *	0	0	1	−1	0	0	1	2 *
Sodium	0.7	FM	136.7	144.8	0.8 *	−0.4	−0.3	0.7 *	1.1 *	0.3	−0.5	−0.3	−0.1	−0.5
TIBC	3	FM	49	83	−	−	−	−	−3	6 *	0	0	2	0
Triglyceride	0.21	FM	0.47	2.60	0.01	0.29 *	0.00	−0.36 *	−	−	−0.04	0.39 *	0.00	−0.26 *
Urate	20.9	F	154	374	−9	20	5	12	−27 *	−8	6	−5	−4	−4
		M	231	475	−21 *	9	−1	0	−	−	14	5	10	−16

TIBC = total iron-binding capacity.
Minus (−) indicates that the number of reference values was too small to allow calculation of reference limits.
An asterisk (*) is used to denote that a difference is large enough to justify partitioning. Partitioning by age is not considered in this table.

TABLE XIV. Differences between mean of reference values on reference individuals with a body mass index (BMI) of <27 kg/m^2 and those with a BMI of ≥ 27 kg/m^2 by gender.

Component			Female						Male					
Name	Goal	Unit	m	Diff.	s	v	n (<27)	n (≥ 27)	M	Diff.	s	v	N	n
Albumin	0.3	g/L	40.7	−0.7	*	*	1240	193	42.2	−0.5	*	*	1027	248
ALP	2.6	U/L	59.8	7.6	*	*	441	69	66.5	2.8		*	365	79
ALT	0.9	U/L	17.6	3.6	*	*	1058	162	23.6	9.4	*	*	875	205
Amylase	3.1	U/L	57.4	−1.7			329	50	60.3	−2.4			275	65
AMY-P	1.8	U/L	29.5	−0.9			253	30	30.5	−5.1		*	180	34
AST	0.7	U/L	21.4	2.1	*	*	983	145	25.3	2.3	*	*	815	197
Bilirubin	0.5	μmol/L	9.8	−0.5		*	1257	191	12.4	−1.0	*	*	1041	249
Calcium	0.012	mmol/L	2.329	−0.008			1182	183	2.352	−0.006			965	239
Calcium corr	0.012	mmol/L	2.342	0.006			1160	183	2.334	0.0055			953	238
Carbamide	0.14	mmol/L	4.61	0.11			1179	167	5.45	0.09			951	236
Cholesterol	0.06	mmol/L	5.21	0.29	*	*	1254	194	5.12	0.40	*	*	1037	248
CK	7.5	U/L	89.5	14.5	*	*	910	138	133.2	19.1	*	*	634	167
Creatininium	1.2	μmol/L	66.3	1.2			1207	184	79.6	0.2			1008	235
Glucose	0.07	mmol/L	4.74	0.28	*	*	421	61	4.95	0.17	*	*	349	87
GT	1.9	U/L	21.8	5.58	*	*	634	94	32.3	5.67	*	*	533	120
HDL-chol.	0.04	mmol/L	1.72	−0.25	*	*	1192	187	1.40	−0.16	*	*	983	239
Iron	1.0	μmol/L	18.9	−1.6	*	*	1065	152	20.5	−0.2			861	212
Iron sat	0.013		0.286	−0.0223		*	259	36	0.317	−0.003			306	62
LD	3	U/L	151	22	*	*	213	31	149	17	*	*	174	41
LDL-chol.	0.10	mmol/L	3.07	0.31	*	*	541	91	3.2	0.31	*	*	423	109
Magnesium	0.008	mmol/L	0.815	0.009		*	996	145	0.830	0.008			800	180
Phosphate	0.021	mmol/L	1.166	−0.060	*	*	1191	174	1.112	−0.032	*	*	987	241
Potassium	0.03	mmol/L	4.06	0.05	*	*	1198	182	4.12	0.07	*	*	985	241
Protein	0.5	g/L	69.4	0.0			885	141	70.5	−0.2			762	196
Sodium	0.3	mmol/L	140.5	0.4	*	*	1218	187	141.3	0.0			989	246
TIBC	1.2	μmol/L	65.6	0.9			262	36	63.4	2.4	*	*	307	63
Triglyceride	0.08	mmol/L	1.00	0.33	*	*	553	92	1.11	0.47	*	*	444	112
Urate	8	μmol/L	246	49	*	*	1210	178	334	28	*	*	995	237

ALP = alkaline phosphatase; ALT = aspartate transaminase; AMY – P = amylase-pancreatic type; AST = aspartate transaminase; CK = creatine kinase; GT = γ-glutamyltransferase; LD = lactate dehydrogenase; TIBC = total iron-binding capacity.

The column titled "Goal" shows the bias goal, calculated as 0.375·biological variation, "m" the mean value for subjects with a BMI of <27 kg/m^2, and "Diff." the mean of results obtained for subjects with a BMI of ≥ 27 kg/m^2 minus the mean of results obtained for subjects with a BMI of <27 kg/m^2.

Asterisk (*) in the column "s" denotes a significant difference ($p<0.05$) and an asterisk in the column "v" means that the absolute value of Diff. exceeds Goal. The column "n" shows the number of reference values in each BMI group.

being Swedish, its suggestions reflect what has recently been considered as appropriate for reference intervals in the Northern countries.

Comments. The continuous decrease in *albumin* concentrations with age is reflected by the recommendation made in this project to partition at the ages of 40 and 70 years. Similar partitioning is also recommended in Tietz, but at the age of 60 years. Overall, the agreement between the results obtained in NORIP and the recommendations of the two textbooks is fairly good.

For bilirubin NORIP recommends an upper limit of 25 μmol/L, which is about 5 μmol/L higher than those recommended in Tietz and Laurell.

For *calcium*, the upper limit recommended by NORIP is in agreement with Tietz but 0.09 mmol/L lower than the corresponding value in Laurell. Tietz gives a higher level by 0.05 mmol/L for the age of >60 years, but such age variation was not observed in the present project. As expected, the age dependence of albumin is reflected in the behaviour of the reference interval for albumin-corrected calcium: its distributions should be partitioned at the age of 50 years. No reference intervals for albumin-corrected calcium are suggested in Tietz or Laurell.

TABLE XV. Reference limits recommended by NORIP for fresh and thawed serum and plasma as compared to suggestions presented in the textbooks of clinical chemistry edited by Tietz and Laurell.

		Reference intervals													
				NORIP					Tietz [15]			Laurell [16]			
Property				Serum		Plasma			Serum			Serum			
Name	Unit	Gender	Age	Low	High	Low	High	Comment	Low	High	Comment	Low	High	Comment
Albumin	g/L	FM	18–39	36	48				35	52	>60 y: 32–46	36	48	
			40–69		45									
			≥70	34										
Bilirubin	μmol/L	FM	≥18	5	25				5	21			20	
Calcium	mmol/L	FM	≥18	2.15	2.51				2.15	2.5	>60 y: 2.2–2.55	2.20	2.60	
Carbamide	mmol/L	F	18–49	2.6	6.4				2.1	7.1	>60 y: 2.9–8.2	3.3	9.7	
			≥50	3.1	7.9									
		M	18–49	3.2	8.1									
			≥50	3.5										
Cholesterol	mmol/L	FM	18–29	2.9	6.1				3.2–3.4	5.6–6.3	Each 5-y period	3.5	8.0	Increase >40 y,
			30–49	3.3	6.9				3.4–4.1	6.0–7.2	and gender			F>M
			≥50	3.9	7.8				3.7–4.5	6.9–7.9				
Creatininium	μmol/L	F	≥18	50	90			See Table XVI	53	97		45	100	
		M	≥18	60	100			and plot of	62	115		55	115	
								enzymatic –,						
								Vitros – and						
								Jaffé methods						
								on NORIP						
								home site [2]						
Glucose	mmol/L	FM	≥18	4.0	6.0	4.2	6.3	Fasting (≥12 h)	4.1	5.9	>60 y: 4.6–6.4,	3.3[1]	5.6[1]	[1]fB, 10–15%
											>90 y: 4.2–6.7			higher in S/P
HDL-chol.	mmol/L	F	≥18	1.0	2.7				0.9–1.0	2.0–2.5	Each 5-y period	0.75	1.90	
		M	≥18	0.8	2.1				0.7–0.8	1.6–1.7	and gender.	0.70	1.60	
Iron	μmol/L	F	≥18	9	34			Results <6 μmol/L	9	30.4		10	29	
		M						removed	12	31		13	36	

TABLE XV. (Continued).

Property		Reference intervals												
				NORIP					Tietz [15]			Laurell [16]		
				Serum		Plasma			Serum			Serum		
Name	Unit	Gender	Age	Low	High	Low	High	Comment	Low	High	Comment	Low	High	Comment
Iron sat.		F	18–49	0.10	0.50			Oestrogen users and iron	0.15	0.50				
			≥50	0.15										
		M	≥18		0.57			<6 μmol/L removed	0.20	0.50				
LDL-chol.	mmol/L	FM	18–29	1.2	4.3			LDL-chol. = cholesterol −HDL-chol. − triglyceride/2, where triglyceride is <4 mmol/L	1.5–1.8	3.8–4.3	Each gender and 5-year period.	2.2	6.2	Increase >40 y, F>M
			30–49	1.4	4.7				1.8–2.5	4.0–5.2				
			≥50	2.0	5.3				2.2–2.6	4.8–5.8				
Magnesium	mmol/L	FM	≥18	0.71	0.94				0.66	1.07		0.7	1.1	
Potassium	mmol/L	FM	≥18	3.6	4.6	3.5	4.4		3.5	5.1		3.5	5.0	
Phosphate	mmol/L	F	≥18	0.85	1.50	0.76	1.41		0.87	1.45	F>60 y: 0.90–1.32, M>60 y: 0.74–1.20			
		M	18–49	0.75	1.65	0.71	1.53							
			≥50		1.35		1.23							
Protein	g/L	FM	≥18	62	78	64	79		64	83	>60 y: 2 lower			
Sodium	mmol/L	FM	≥18	137	145		144		136	145		136	146	
TIBC	μmol/L	FM	≥18	49	83	47	80	Oestrogen users removed	44.8	71.6		46	70	
Triglyceride	mmol/L	F	≥18	0.45	2.60			Fasting (>=12 h)	0.41 –0.59	1.63–2.62	Gender and age (each decade) partitioning. Increasing with age.	0.4	1.6	Increase >40 y
		M							0.50 –0.62	2.27–3.70				
Urate	μmol/L	F	18–49	155	350				130	390	F>60 y: 200–430, M>60 y: 250–470	120	340	
			≥50		400									
		M	≥18	230	480							160	450	

NORIP = Nordic Reference Interval Project; TIBC = total iron-binding capacity; F = female, M = male, y = years, Low = lower reference limit, High = upper reference limit.

For *carbamide* (urea), partitioning by both gender and age (at 50 years) is suggested by NORIP, but no stratifications are recommended in Laurell. Tietz does not suggest partitioning by gender. The lower limit is in agreement with Laurell and the upper limit with Tietz.

For *cholesterol*, showing increasing concentrations with age, NORIP recommends partitioning by age 30 and 50 years, whereas Tietz suggests partitioning into age intervals of 5 years. Laurell suggests a slightly higher upper limit and comments that increased concentrations are to be expected for ages of >40 years, for women as compared to men.

The gender-specific reference intervals recommended for *creatinine* by NORIP agree well with both Tietz and Laurell in the cases of both genders as far as the lower reference limit is concerned, but for the upper limit, these textbooks suggest a value that is higher than that obtained in the present project by about 10 and 15 μmol/L for women and men, respectively. The main reason for this disagreement is that the limits presented in Tietz and Laurell are based on the Jaffé method, while the reference values of NORIP were corrected to correspond to the reference method for creatininium.

For *glucose*, separate fasting reference intervals for serum (4.2–6.3 mmol/L) and plasma (4.0–6.0 mmol/L) were obtained in the present project. To calculate these intervals, reference values consistent with the definition of diabetes were excluded (i.e. values of >11.0 mmol/L obtained without fasting and those of >7.0 mmol/L obtained after fasting of >=12 h). Tietz suggests a reference interval for serum glucose which is narrower by 0.1 mmol/L at each end, and higher values for subjects >60 and >90 years of age (two different intervals for older age). The suggestion in Laurell is in reasonable agreement with those presented in Tietz and in this project.

For *HDL-chol.*, Tietz suggests partitioning into age intervals of 5 years, and Laurell presents reference limits that are markedly lower than those obtained in NORIP: at the lower end by 0.25 mmol/L for women and by 0.1 mmol/L for men, and at the upper end by 0.8 mmol/L for women and by 0.5 mmol/L for men. The methods used in NORIP were mostly direct wet chemistry methods (89) with the exception of one precipitation method, but also some (6) dry chemistry (Ortho) methods were used.

For *iron*, NORIP does not suggest partitioning by gender while both Tietz and Laurell do. The lower limit obtained in NORIP lies close to those recommended in both Tietz and Laurell, but the suggestions for the upper limit vary between 29 and 36 μmol/L.

For *iron saturation*, NORIP recommends partitioning by age, in contrast to Tietz, while both recommend partitioning by gender. The limits suggested by Tietz for women are identical with the NORIP limits for women of age >50 years. Men have about 5% (in absolute terms) higher values than women.

For *LDL-chol.*, Laurell suggests considerably higher values than NORIP. As opposed to Tietz, NORIP does not recommend partitioning by gender. While Tietz suggests partitioning into age intervals of 5 years, partitioning by age at the ages of 30 and 50 years is recommended by NORIP. Laurell comments that increased values are observed for ages of >40 years, and for women as compared with men.

For *magnesium*, the lower limit obtained in NORIP is almost identical with the suggestion in Laurell but 0.05 mmol/L higher than that in Tietz. Both Tietz and Laurell present an upper limit that is about 0.15 mmol/L higher than that recommended by NORIP.

For *potassium*, NORIP and both textbooks recommend separate reference intervals for serum and plasma. The plasma intervals are almost identical, but a higher upper limit for serum than for plasma of about 0.5 mmol/L is suggested by both Tietz and Laurell, whereas these limits were much closer to each other in the present project (Table XVI). The recommendations made in Tietz and Laurell for serum potassium might reflect excessive concentrations caused by leakage of potassium from cells to plasma before centrifugation, which is a well-known source of preanalytical

TABLE XVI. Reference intervals for potassium (mmol/L) from different sources.

	NORIP	Tietz [15]	Laurell [16]
Serum	3.6–4.6	3.5–5.1	3.5–5.0
Plasma	3.5–4.4	3.4–4.4	3.5–4.5

error for this measurement. Preanalytical treatment of samples was probably closer to ideal circumstances in the present project than what is normally achieved.

For *phosphate*, NORIP and Tietz suggest partitioning by both gender and age. However, the recommendation to partition by gender in Tietz only concerns ages of >60 years. NORIP does not suggest partitioning by age for women. For men, there is a continuous decrease with age of the upper limit from approximately 1.7 mmol/L to 1.4 mmol/L, but a similar trend was not observed for women. The intervals presented for men in Tietz are narrower than those obtained in NORIP, the upper limit being about 0.2 mmol/L lower and the lower limit about 0.1 mmol/L (this is true for men <60 years) higher. In contrast, the interval recommended for women <60 years in Tietz is in agreement with the corresponding interval obtained in NORIP. NORIP proposes different intervals for serum and plasma (slightly lower levels for plasma).

For *protein*, Tietz suggests 2 and 5 g/L higher values for the lower and the upper reference limits, respectively, than were obtained in NORIP, but comments that the concentrations are lower by 2 g/L for ages >60 years.

For *sodium*, the suggestion in Tietz for the lower limit lies 1 mmol/L below that recommended by NORIP, and Laurell suggests an interval that is broader by 1 mmol/L at both ends.

For *TIBC*, Tietz and Laurell recommend clearly smaller values than NORIP, by about 4 μmol/L for the lower limit and 12 μmol/L for the upper limit. The traceability of TIBC in the present project is based on the median value of CAL as calculated from the means for that control material obtained in those laboratories, which measured transferrin (in g/L) by using an immunological method together with IFCC calibration. The transferrin concentrations were converted to TIBC by multiplying by the factor of 25.1, which is applied by nearly all laboratories using this method to estimate TIBC in μmol/L (the value of 25.1 is based on a molecular weight of 79 680 daltons for transferrin).

The upper limit for *triglyceride* obtained in NORIP is substantially (by 1 mmol/L) higher than that recommended in Laurell. Laurell comments, however, that triglyceride levels are increased after 40 years of age, and the upper limits recommended in Tietz for subgroups representing such ages are even higher, particularly for men, than that obtained in the present project (2.6 mmol/L).

For *urate* (uric acid), NORIP and both textbooks recommend partitioning by gender, but Tietz does not suggest such partitioning for subjects <60 years. Laurell does not recommend partitioning by age, as opposed to Tietz and the present project, which report on higher levels for older age groups.

DISCUSSION

Selection of reference individuals [3]

Ideally, reference individuals should be selected randomly from the entire population, to which new reference intervals will be applied. This principle was not rigorously followed in the present project, however.

- Reference individuals were selected from readily available individuals in the local surroundings of the participating laboratories. This recruitment policy might lead to sample deviation, although we are not aware of any major bias-generating factors that could reduce the generalizability of the results obtained in this project.
- The relative numbers of reference individuals recruited from each participating country are not consistent with the populations in the respective countries. Sweden deviates most in this respect.
- The age distribution of reference individuals is not in agreement with that of the populations in the Nordic countries, either, because the protocol of this project aimed at obtaining equal numbers of subjects in each age group. This discrepancy might affect the suggested stratifications (Table XII) to some extent, but because software for prevalence corrections in the case of several subgroups is at this moment not available, it is not possible to examine this issue in more detail.

The prevalence effect is discussed in theoretical terms in a recent publication [17] and illustrated as applied to stratification by countries in the cases of some enzymes using the data of this project by Lahti [14].

Analytical methods

Traceability. At the start of this project it was not clear how measurement of project samples using many different routine methods instead of one reference method would affect calculated reference intervals. Therefore, it was essential to use calibrator and control materials with the highest quality possible, to be measured together with the project samples. What was especially important was that these materials were commutable, to correct for laboratory and method biases. In order for the method manufacturers and the laboratories to accept possible deviations found for methods, it was also essential that the target values set on the project "calibrator" were traceable to the highest metrological order. Judging by the results, it seems that this objective of the project was successfully achieved. Another factor of importance is that the target value of the "calibrator" should have been relatively high for each component. This requirement was satisfied for non-enzymes with the exception of bilirubin. For this property, however, the reference limits turned out to be almost the same irrespective of whether correction was applied or not. The reference intervals for properties with narrow reference intervals are consistent with or in some cases (sodium) even narrower than those quoted by established literature references. One consequence of introducing a reference material with the rare combination of being highly commutable and at the same time traceable to the highest metrological order with very small uncertainties is that both the laboratories and the method manufacturers will have to investigate any important biases revealed by using this control. It will be interesting to follow what the effects of offering this material commercially will be on the results from external quality assessment programs in the Nordic countries.

Correction for between-series variation. The procedure used in this project to perform the analytical measurements involves the within-series analytical variation, because only one measurement of each reference sample was made, but not the between-series variation. This component could be accounted for (it would probably be worthwhile making such an adjustment in the cases of, e.g., sodium, calcium and potassium) either by measuring the reference samples over several days, or by adding a representative between-series variation as a random number to all reference values.

Evaluation of method quality. The control P is a serum pool from women using contraceptives and was included in the project because of the somewhat different characteristics than those of the other controls. In general, however, it was not possible to see any characteristic effect of this control as compared with the other controls. Without going into details concerning evaluation of each property and laboratory on the basis of the quotient HIGH/LOW, supposed to be equal to 2.0 (except sodium and calcium), we calculated reference intervals before and after removing laboratories with the largest deviations, but did not observe any important changes in the results [18]. For this reason we did not eliminate laboratories with slightly deviating corrected control values. The statistical quality of reference limits calculated for subgroups will thereby be improved because of increased numbers of reference values in each subgroup. In this project, no further comparisons between methods (samples run in parallel on varying measurement systems) were made.

Calculation of reference intervals

The RefVal 4.0 program calculates reference intervals using three different methods: the simple non-parametric, the bootstrap non-parametric, and the parametric methods. The parametric method uses a two-step transformation procedure to normalize a distribution. As there were many occasions where this procedure did not succeed in normalizing the obtained data distributions, the project group decided to perform the calculations by applying the simple non-parametric method throughout this project, irrespective of the form of a particular distribution. Even if some researchers might prefer the non-parametric bootstrap method, which gives slightly narrower confidence intervals for reference limits, our experience is that the simple non-parametric and the bootstrap non-parametric methods give much the same results.

There are many methods proposed for calculating cumulative probabilities (P) from

rank numbers (r), e.g. $P = r/(n+1)$, $P = (r-0.5)/n$, and $P = (r-1)/(n-1)$, where n is the number of observations in a distribution. To calculate percentiles from P, application of linear interpolation may be required (in cases where the rank is not an integer), and tied (equal) reference values may also complicate the calculations. When a distribution has a very long tail, as was the case for CK in this project, with single observations dispersed over a wide range, the differences between calculation methods may appear considerable even if the distribution contains a large number of samples. As compared to confidence intervals, these differences were not important, however.

During this project, an (it is hoped) improved method for partitioning reference data into subgroups was developed [7, 17] and used. The conclusions obtained by applying this method were adopted in most cases, with exceptions made occasionally where the clinical need for partitioning seemed limited.

Many aspects of the project data have so far not been investigated thoroughly. These include relationships between reference values and much of the information from the project questionnaire, e.g. biological, geographical and sample collection parameters of each individual. Gender, age BMI and, to a certain extent, fasting are parameters that have already been considered, but parameters not mentioned specifically have not been examined systematically. Relationships between different properties are an issue that was not investigated either.

One question that needs to be considered when attempting to establish common reference intervals for several countries is whether these intervals truly are common or not [14]. This question seems to be particularly relevant for Iceland, which showed for many properties country-specific reference intervals that deviated from those of the other countries, although these deviations were not necessarily dramatic, as shown in Table XIII. However, the numbers of reference values obtained from this country being small as compared to the other countries, the statistical uncertainty of its country-specific reference intervals is relatively large, while its influence on the common distributions remains limited. Hence, because neither lifestyle factors nor genetic background seems to require exclusion of Iceland, the project group recommends application of the calculated common reference intervals in all of the five Nordic countries.

Introducing the new reference intervals

One aim of the project design was to engage as many of the major Nordic clinical laboratories as possible in the production of the new reference intervals and thereby, in turn, to facilitate their adoption into clinical use. The Nordic societies of clinical biochemistry together with their umbrella organization, the Nordic Society of Clinical Chemistry (NFKK), have also contributed by taking the necessary initiatives to introduce the common reference intervals produced by this project. The new reference intervals for enzymes are already in use in Norway (May 2003) and in Denmark (from December 2003). Intervals for all properties will be introduced throughout the Nordic countries during 2004.

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